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A FURTHER STUDY OF THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) UPON THE EXPERIMENTAL CARDIOVASCULAR LESIONS PRODUCED BY ANAPHYLACTIC HYPERSENSITIVITY

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Received for publication October 10, 1950

In a previous study from this laboratory (1) it was reported that the adrenocorticotropic hormone of the pituitary (ACTH) inhibited the development of the experimental cardiovascular lesions (periarteritis nodosa, cardiac inflammatory lesions) that Rich and Gregory (2, 3), in experiments confirmed by many investigators, have shown to be producible by anaphylactic hypersensitivity. In that study, 18 of 20 animals subjected to the serum sickness type of protracted anaphylactic reaction developed well-marked cardiovascular lesions, whereas such lesions appeared in only 5 of 20 animals sensitized and exposed to the antigen in the same manner, but treated with ACTH. While this difference was a striking one, it was believed advisable to extend the study; for it is now well known that individual animals of a given species, as well as individual human beings, differ markedly and unpredictably in their tendency to develop lesions due to hypersensitivity on contact with the specific antigen to which they are sensitized. For that reason, the present additional study was carried out. The results of this study support completely those of the former one. Again, in this series, cardiovascular lesions occurred in a much lower percentage of the animals treated with ACTH than in the untreated controls.

EXPERIMENTAL PROCEDURE

In this study, 60 male albino rabbits were used. They were divided into three groups of 20 animals each, averaging 2600–2800 grams in weight (Table I). Under ether anesthesia, using 30 gauge short-bevel needles, each animal was given an intracorneal injection of sterile horse serum (without preservative)[1] in the right

[1] The horse serum was very kindly supplied by Sharp and Dohme, Inc.

TABLE I

Weights of Adrenals and Thymus with Ratio of Each to Body Weight

INTRAVENOUSLY AND INTRACORNEALLY SENSITIZED, ACTH TREATED						INTRAVENOUSLY AND INTRACORNEALLY SENSITIZED, UNTREATED						INTRACORNEALLY SENSITIZED, UNTREATED					
Rabbit	Body wt. at autopsy	Wt. of adrenals	Adrenal / Body × 1000	Wt. of thymus	Thymus / Body × 1000	Rabbit	Body wt. at autopsy	Wt. of adrenals	Adrenal / Body × 1000	Wt. of thymus	Thymus / Body × 1000	Rabbit	Body wt. at autopsy	Wt. of adrenals	Adrenal / Body × 1000	Wt. of thymus	Thymus / Body × 1000
	gms.	*mgm.*		*gms.*			*gms.*	*mgm.*		*gms.*			*gms.*	*mgm.*		*gms.*	
81	2950	310	.11	2.2	0.74	101	3100	470	.15	8.5	2.74	301	2225	204	.09	7.7	3.45
82	2450	614	.25	3.7	1.51	102	3250	276	.085	4.7	1.45	302	2275	239	.10	3.6	1.58
83	2825	122	.04	6.2	2.20	103	2625	286	.11	7.0	2.66	303	2925	208	.07	6.5	2.21
84	2300	151	.07	3.4	1.48	104	3600	440	.12	5.8	1.61	304	2100	175	.08	4.0	1.90
85	2775	143	.05	5.3	1.91	105	2300	162	.70	4.1	1.78	305	3800	199	.05	4.3	1.13
86	2375	195	.08	4.8	2.02	106	3150	219	.066	7.9	2.50	306	3250	335	.10	4.5	1.38
87	2900	247	.085	2.8	0.97	107	3275	145	.04	5.0	1.53	307	2350	110	.05	0.5	0.21
88	3125	560	.18	4.2	1.34	108	2875	233	.08	6.8	1.36	308	2775	159	.06	5.7	2.06
89	2700	242	.09	6.2	2.30	109	2850	300	.105	7.1	2.50	309	2650	187	.07	2.4	0.91
90	2425	362	.15	3.6	1.48	110	2425	215	.09	3.1	1.28	310	2775	246	.09	6.2	2.24
91	3150	211	.067	6.4	2.03	111	2800	204	.07	8.9	3.18	311	2375	314	.13	3.2	1.35
92	2625	146	.055	4.1	1.62	112	2550	349	.14	4.4	1.73	312	2200	235	.11	4.4	2.00
93	2700	217	.08	4.5	1.67	113	2650	187	.07	6.5	2.45	313	2350	240	.10	5.2	2.20
94	2450	312	.13	6.1	2.50	114	2525	308	.12	5.6	2.22	314	2550	177	.07	4.4	1.73
95	2100	305	.145	2.9	1.38	115	2525	140	.06	6.2	2.45	315	2650	239	.09	3.4	1.28
96	2650	201	.076	4.1	1.55	116	2350	217	.09	4.6	1.96	316	2275	131	.06	2.7	1.19
97	2525	357	.14	0.5	0.19	117	2525	199	.08	6.9	2.73	317	2800	152	.05	4.7	1.68
98	2775	219	.08	3.6	1.30	118	2900	212	.07	7.0	2.41	318	2450	581	.24	4.5	1.84
99	2300	440	.19	—	—	119	3050	287	.09	9.5	3.11	319	3250	249	.08	4.0	1.23
100	2450	179	.073	3.6	1.47	120	3000	326	.11	5.8	1.93	320	3550	188	.05	5.8	1.63
Average	2627	271.6	.103	4.10	1.56	Average	2816.2	258.7	.09	6.27	2.23	Average	2678.8	230.4	.085	4.38	1.63

eye, and an intracorneal injection of killed tubercle bacilli in the left eye. The tubercle bacilli were prepared by grinding into suspension 70 mgm. of dried, heat killed, Saranac R1 tubercle bacilli in 5 cc. of normal saline and centrifugalizing for 5 minutes at 800 r.p.m. The supernatant suspension was used for the injections. In each case, an amount of serum or suspension of bacilli sufficient to produce a circular opacity about 4 mm. in diameter ($\frac{1}{40}$–$\frac{1}{60}$ cc.) was injected into the cornea overlying the pupil.

Two days after the intracorneal injections had been made, each of 40 animals, comprising two groups, was given a single intravenous injection of 10 cc. of sterile horse serum (without preservative) per kilogram of body weight. On the same day, and daily thereafter until the end of the experiment, 20 of the intravenously injected animals received 2.5 mgm. of ACTH[2] in 1 cc. of normal saline intramuscularly every 6 hours, a total of 10 mgm. daily. The ACTH (Armour's Lot 77-S) had a potency of 41% of the Armour Standard La-I-A, and contained 0.002 oxytocic units per milligram. The solution of ACTH was prepared fresh every day, as described previously (1). The remaining 40 animals received no treatment.

There were thus three groups of 20 animals each. One group received intravenously 10 cc. of horse serum per kilogram of body weight and was treated daily with ACTH; the second group received the same amount of horse serum intravenously, but received no ACTH; and the third group received neither horse serum intravenously nor ACTH. This latter group, however, as did every animal in each group, received a single intracorneal injection of horse serum in one eye and of killed tubercle bacilli in the other eye at the beginning of the experiment.

The animals were kept in separate cages in the same room, and were given an unrestricted amount of Purina Rabbit Chow Checkers and water. No supplement of fresh vegetables was given.

Beginning on the fifth day after the intracorneal injections of horse serum and tubercle bacilli, the eyes of all animals were examined daily for the occurrence of scleral hyperemia and clouding or vascularization of the cornea.

On the twelfth day after the intravenous injection of horse serum and the fourteenth day after the intracorneal injections, all animals were tested for hypersensitivity to horse serum by the intradermal injection of 0.1 cc. of undiluted horse serum. In addition, 13 animals from each group were given at the same time an intradermal injection of 10.0 mgm. of Old Tuberculin.

On the fourteenth day after the intravenous injection of horse serum the animals of each series were killed by intravenous nembutal after withdrawing blood by cardiac puncture for serological tests. Ring tests for the presence of antibody were performed by layering serial dilutions of horse serum over the undiluted serum to be tested, in tubes 3 mm. in diameter. Tests for the residue of antigen in the circulation were performed by layering serial dilutions of the serum to be tested over an undiluted antiserum prepared by injecting a rabbit intravenously every other day, for three injections, with 1 cc. of horse serum. The rabbit was bled three weeks

[2] We are indebted to Dr. Edwin E. Hays of Armour and Co. for supplying the ACTH.

after the last injection. The serum gave a heavy ring with a 1:25,000 dilution of horse serum.

Careful autopsies were performed on all animals. Sections for the microscopic study summarized in Table III were made from Zenker-formol fixed blocks of the heart, liver, spleen, pancreas, both adrenals, both kidneys, bone marrow, horse serum skin-test site and eyes of each animal. Supplementary blocks of these and other tissues were fixed in Zenker-formol and 10% formalin and preserved for additional study. An equal number of sections of the organs of each animal were prepared and thoroughly searched for lesions. The sections of the corresponding organs of all animals were of approximately the same size. Through a mischance, important tissues from two animals which had received horse serum intravenously were lost. One of these had been treated with ACTH; the other was untreated. Both are omitted from Table III, leaving 19 animals in each of the respective groups.

RESULTS

The results of the *skin tests* are presented in Table II. The treatment with ACTH did not suppress the cutaneous reactions, though, as in the previously reported study (1), the average size of the reactions in the treated animals was slightly smaller than in the untreated, intravenously sensitized animsls. The difference is not at all impressive. Indeed, there were more hemorrhagic reactions in the ACTH-treated group. There were no significant differences in the microscopic character of the skin reactions in the treated as compared with those in the untreated animals. The average size of the reactions in the untreated animals that were sensitized to horse serum by intracorneal injection alone was larger than that in the untreated group that was sensitized by both the intracorneal and the intravenous route; and though there were marked individual differences, the largest lesions occurred in the former group and there were more large lesions in that group. Thus, 8 of the intracorneally sensitized animals had skin reactions six centimeters or larger in diameter, whereas only one of the intracorneally and intravenously sensitized group had a reaction of that size; and 5 of the former had reactions over seven centimeters in diameter, whereas none of the latter had a reaction of that size.

The results of the *precipitin tests for circulating antibody and antigen* are presented in Table III. There was a slight, but not at all impressive, tendency for the titers to be lower in the ACTH-treated group There was a more definite tendency for the precipitin titers of the animals sensitized by intracorneal injection alone to be higher than those of the group that received both intracorneal and intravenous

TABLE II

Local Reactions in mm. 24 Hours After Intradermal Injection of 0.1 cc. of Horse Serum on 12th Day After Intravenous and 14th Day After Intracorneal Sensitizing Injection

RABBIT	INTRAVENOUSLY AND INTRACORNEALLY SENSITIZED, ACTH TREATED	RABBIT	INTRAVENOUSLY AND INTRACORNEALLY SENSITIZED, UNTREATED	RABBIT	INTRACORNEALLY SENSITIZED, UNTREATED
81	60 x 40 pink edema	101	45 x 35 pink edema	301	45 x 40 pink edema
82	35 x 35 pink edema	102	50 x 45 pink edema 10 x 10 red center	302	35 x 35 pink edema 15 x 15 red center
83	30 x 30 pink edema	103	55 x 45 pale edema	303	40 x 40 pink edema
84	55 x 40 pink edema 10 x 10 red center	104	55 x 40 pink edema 15 x 15 red center	304	110 x 80 pink edema 12 x 12 hemorrhage
85	50 x 45 pink edema	105	35 x 25 pink edema	305	115 x 110 pale edema
86	30 x 25 pale edema	106	50 x 45 pink edema	306	30 x 25 pink edema diffuse petechiae
87	65 x 60 pink edema	107	40 x 40 pink edema 10 x 10 red center	307	90 x 50 pink edema
88	70 x 65 pink edema	108	40 x 40 pink edema 15 x 15 red center	308	65 x 45 pink edema 20 x 10 hemorrhage
89	40 x 40 pink edema	109	55 x 45 pink edema	309	65 x 50 pink edema
90	60 x 50 pink edema 10 x 10 red center	110	40 x 35 pink edema	310	60 x 40 pink edema
91	35 x 35 pink edema 15 x 15 red center	111	40 x 35 pink edema	311	55 x 40 pink edema
92	30 x 25 pink edema 15 x 15 red center	112	35 x 32 pink edema	312	50 x 35 pink edema
93	25 x 25 pink edema 10 x 10 red center small hemorrhage	113	40 x 35 pink edema 10 x 10 hemorrhage	313	110 x 90 pink edema 10 x 10 red center
94	25 x 20 pale edema 10 x 10 hemorrhage	114	60 x 50 pink edema	314	55 x 45 pink edema 10 x 10 red center
95	25 x 25 pink edema 10 x 10 hemorrhage	115	50 x 45 pink edema	315	45 x 40 pink edema

TABLE II—*Continued*

RABBIT	INTRAVENOUSLY AND INTRACORNEALLY SENSITIZED, ACTH TREATED	RABBIT	INTRAVENOUSLY AND INTRACORNEALLY SENSITIZED, UNTREATED	RABBIT	INTRACORNEALLY SENSITIZED, UNTREATED
96	70 x 50 pink edema	116	50 x 50 pink edema 10 x 10 red center	316	35 x 35 pink edema diffuse petechiae
97	30 x 30 pink edema 10 x 10 hemorrhage	117	55 x 50 pink edema	317	40 x 35 pink edema
98	40 x 30 pink edema 10 x 10 red center	118	40 x 35 pink edema 10 x 10 red center	318	25 x 25 pink edema
99	20 x 20 pink edema	119	55 x 50 pink edema 10 x 10 purple center	319	45 x 35 purple edema
100	45 x 40 pink edema 7 x 7 hemorrhage	120	55 x 45 pink edema	320	75 x 60 pink edema 10 x 10 red center
	Average: 42 x 36 edema 2 pale edema 18 pink edema 6 red center 5 hemorrhage		*Average:* 47 x 41 edema 1 pale edema 19 pink edema 6 red center 1 purple center 1 hemorrhage		*Average:* 59 x 47 edema 1 pale edema 18 pink edema 4 red center 1 purple edema 4 hemorrhage

sensitizing injections. As in our previous studies (1, 5), there was no parallelism between the titer of circulating antibody or antigen and the development of the cardiovascular lesions (see Table III). This re-emphasizes the fact that in the experimental animal, as in the human being, host factors that are not yet understood play a highly important rôle in determining whether the presence of antibody and antigen will incite the development of visceral lesions.

The results of the *intracorneal test injections* of horse serum conformed with those reported in our previous study (5) in that the animals that received an intravenous injection of horse serum in addition to the intracorneal injection failed to develop the clouding of the cornea by inflammatory exudate which, as Wessely demonstrated years ago (4), appears at the end of the second week after the introduction of foreign protein into the cornea of otherwise untreated animals. This late corneal flare-up reaction is doubtless due to the persistence of a

TABLE III

Intravenously and Intracorneally Sensitized, ACTH Treated

RABBIT	ANTIBODY TITER	ANTIGEN TITER	PERIARTERITIS NODOSA	ENDOCARDITIS
81	1:3200	0	0	0
82	1:6400	1:400	+	0
83	1:3200	1:10	0	0
84	1:3200	1:200	0	0
85	1:6400	1:400	0	0
86	1:3200	1:800	0	0
87	1:6400	1:100	+	+
88	1:3200	1:800	0	0
89	1:6400	1:400	0	0
90	1:6400	1:200	+	+
91	1:6400	0	+	0
92	1:6400	1:1	0	0
93	1:6400	1:400	0	0
94	1:12,800	0	+	0
95	1:12,800	0	0	0
96	1:6400	1:200	0	0
97	1:6400	1:800	0	0
98	1:3200	1:800	0	0
99	1:3200	1:800	0	0
Total			5 (26%)	2 (10%)

TABLE III—*Continued*

Intravenously and Intracorneally Sensitized, Untreated

RABBIT	ANTIBODY TITER	ANTIGEN TITER	PERIARTERITIS NODOSA	ENDOCARDITIS
101	1:6400	1:400	+	0
102	1:6400	1:200	0	0
103	1:6400	1:200	+	0
104	1:6400	0	+	+
105	1:6400	1:800	+	0
106	1:12,800	1:800	+	0
107	1:6400	1:1	+	+
108	1:12,800	1:200	+	0
110	1:6400	1:800	+	0
111	1:3200	1:800	+	0
112	1:3200	1:800	0	0
113	1:6400	1:400	+	0
114	1:25,600	0	+	0
115	1:6400	1:400	+	0
116	1:12,800	1:10	0	0
117	1:6400	1:400	+	+
118	1:12,800	0	+	+
119	1:6400	1:800	+	0
120	1:6400	1:800	+	0
Total			16 (84%)	4 (21%)

TABLE III—*Concluded*

Intracorneally Sensitized, Untreated

RABBIT	ANTIBODY TITER	ANTIGEN TITER	PERIARTERITIS NODOSA	ENDOCARDITIS
301	1:3200	0	0	0
302	1:6400	0	0	0
303	1:3200	0	0	0
304	1:25,600	0	0	0
305	1:12,800	0	0	0
306	1:12,800	0	0	0
307	1:12,800	0	0	0
308	1:25,600	0	0	0
309	1:800	0	0	0
310	1:12,800	0	0	0
311	1:6400	0	0	0
312	1:6400	0	0	0
313	1:25,600	0	0	0
314	1:6400	0	0	0
315	1:3200	0	0	0
316	1:25,600	0	0	0
317	1:12,800	0	0	0
318	1:3200	0	0	0
319	1:25,600	0	0	0
320	1:6400	0	0	0

residue of the antigen in the cornea or limbus, which sets the stage for a local antigen-antibody inflammatory reaction when antibody formation, engendered by antigen absorbed from the cornea, has proceded to a sufficient degree. The flare-up corneal reaction occurred in all of the twenty animals of the group that received an intracorneal injection of horse serum with no additional intravenous injection of serum. Since the intravenous injection, itself, suppressed the reaction, the effect of ACTH in inhibiting the reaction cannot be ascertained from the material of the present experiment, for all animals that recieved ACTH also received horse serum intravenously.

The purpose of the injection of killed tubercle bacilli into the cornea of one eye of each of the animals was to provide a stimulus for corneal vascularization, in order to study the effect of ACTH upon the growth of capillaries in a site favorable to minute, direct observation. The suspension of bacilli used was of insufficient density to incite corneal vascularization in the majority of the animals that received no ACTH.

There is, therefore, an inadequate basis of comparison for determining any relative degree of inhibition of capillary proliferation that ACTH may produce. However, it can be stated that capillary proliferation was not prevented by the dose of ACTH used, which was equivalent by body weight to 165–285 mgm. daily for a human being weighing 132 lbs. Marked corneal vascularization occurred in a number of the ACTH-treated animals. The effect of the adrenal cortical hormone upon the corneal flare-up reaction and upon the proliferation of capillaries into the cornea is at present under investigation in this laboratory.

Table III presents the occurrence of *cardiovascular lesions* of hypersensitivity in the three groups. The lesions (periarteritis nodosa, endocarditis) were of the type amply illustrated in other publications from this laboratory (2, 3). No lesions developed in the group sensitized by intracorneal injection, and that is to be expected; for the development of the lesions depends upon the meeting of antigen and antibody in the tissues, and there was no residue of antigen in the circulation after antibody had developed in this group. Eighty-four per cent of the intravenously sensitized, untreated animals developed cardiovascular lesions, whereas they were present in only 26 per cent of the animals treated with ACTH. These figures are closely similar to those in the previous study (1), in which 90 per cent of the untreated animals developed the lesions, and only 25 per cent of the ACTH-treated ones. In our study in which cortisone was used instead of ACTH, 85 per cent of the untreated animals developed the lesions, whereas they occurred in only 20 per cent of the cortisone-treated animals (5). Considering the individual differences in host-reactivity that affect the development of lesions due to hypersensitivity, there is a rather remarkable consonance between the figures in these three separate studies, which comprise a total of 118 intravenously sensitized animals, half of them treated with ACTH or cortisone, and half untreated. The results indicate plainly that both ACTH and cortisone exert a decidedly inhibitory effect upon the development of the cardiovascular lesions of hypersensitivity.

Acute glomerulonephritis occurred in 9 of the intravenously sensitized animals and in only 4 of the ACTH-treated group. In our previous study, glomerulonephritis occurred in 15 of 20 intravenously sensitized untreated animals and in only 4 of 20 similarly sensitized animals

treated with ACTH. The effect of ACTH and of cortisone in inhibiting the development of the glomerulonephritis caused by hypersensitivity has been discussed briefly in a preceding paper (5), and will be detailed in a separate report.

The *adrenals* of all but two of the ACTH-treated animals showed a loss of cortical lipoid to a degree that was clearly evident in even the hematoxylin-eosin sections. The lipoid depletion was marked in 15 animals (Figures 1 and 2), and moderate in 3. Sayers and his co-workers (6) found that ACTH caused depletion of the cortical lipoid, just as do non-specific stress stimuli. Selye (9), on the other hand, has recently stated that in his experience ACTH does not reduce the cortical lipoid in either acute or chronic experiments and, since stress stimuli do cause a reduction of cortical lipoid, he suggests that stress stimuli may cause a discharge from the pituitary of a corticotropic principle different from ACTH. The striking depletion of cortical lipoid in the present experiment and in the ACTH-treated animals of our previous study (1) is in accord with the observations of Sayers and his co-workers, and provides clear evidence that ACTH, itself, causes a depletion of cortical lipoid.

Several years ago it was shown by one of us (7) that severe acute infections not infrequently produce a peculiar and severe type of damage to the adrenal cortex, which was termed "tubular degeneration," and that this cortical damage, when extensive, is commonly associated with peripheral circulatory collapse. That the adrenal damage may be responsible for the circulatory collapse and is not produced by it was indicated by the fact that the lesion occurs in lesser degrees of extensiveness in infections in the absence of peripheral circulatory failure, and by the fact that peripheral circulatory failure (surgical and traumatic shock), even when protracted, does not produce the lesion in the absence of infection. It has been suggested by others that this adrenal lesion may result not from a noxious action of the infection itself, but from overstimulation of the adrenals under the stress of the infection. Selye (9) pictures a lesion that is similar, but divergent in several important respects, which he produced in the rat by injections of a suspension of beef anterior pituitary in saline. Ingle (10) has pointed out that pituitary glands are heavily charged with bacteria when they come from the slaughter house, and that both he

and Selye found that such suspensions produce abscesses. It is pertinent to the question to point out that in this and in our previous study with ACTH (1) the adrenals of the ACTH-treated animals showed not the slightest suggestion of any stage of the process of tubular degeneration though they were subjected continuossly to marked overstimulation, for a period of two weeks.

The *livers* of the ACTH-treated animals showed no marked increase in glycogen such as was encountered in our cortisone-treated animals (5) and in our previous study in which ACTH was used (1). In the latter study a larger dosage of a different preparation of ACTH was used. The livers of about half the ACTH-treated animals in the present experiment contained small fat droplets, but the fat deposits were less than in many of the animals in our previous ACTH and cortisone experiments.

The *spleens* of the ACTH-treated animals showed no striking depletion of lymphoid tissue. The spread of lymphoid tissue into the pulp, which results from the parenteral introduction of foreign protein into the body (8), was not suppressed to the same degree as in our previous experiments with ACTH and with cortosone, nor was extramedullary blood formation in the spleen as prominent as in those experiments. These differences, as in the case of glycogen and fat deposits in the livers, are probably referable to the differences in dosage.

CONCLUSIONS

This report deals with the effect of pituitary adrenocorticotropic hormone (ACTH) upon a second series of rabbits sensitized with horse serum in the manner that favors the development of periarteritis nodosa and cardiac inflammatory lesions. Sixteen of nineteen sensitized, untreated animals developed cardiovascular lesions of this type, whereas the lesions occurred in only 5 of 19 sensitized animals treated with ACTH.

This study, together with our previous observations on the effect of ACTH and of cortisone in similarly sensitized animals, provides substantial evidence that both ACTH and cortisone exert an inhibitory effect upon the development of the cardiovascular lesions of hypersensitivity. In these three separate studies, cardiovascular lesions occurred in 51 of 59 sensitized, untreated animals, and in only 14 of 59 sensitized animals treated with ACTH or cortisone.

The mechanism by means of which this inhibitory effect operates is obscure at present.

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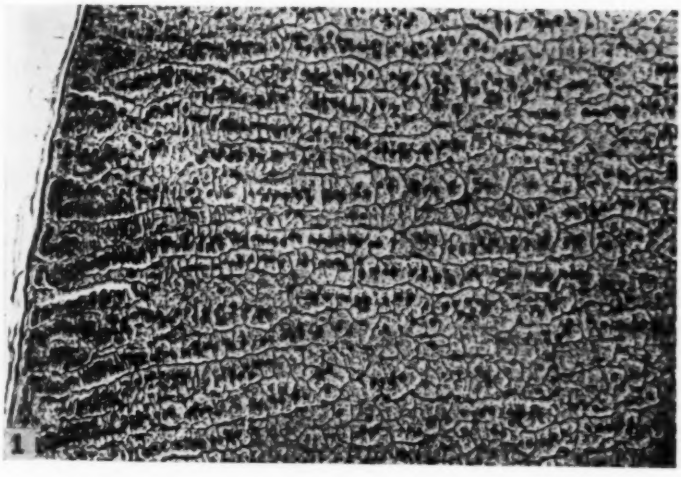
Explanation of Illustrations

(Photographs by Miss Joan Wheaton)

Figure 1. Adrenal of sensitized, untreated rabbit No. 113. The cells of the fasciculate zone are normally distended with lipoid.

Figure 2. Adrenal of sensitized, ACTH-treated rabbit No. 97. The cortical cells have lost their lipoid.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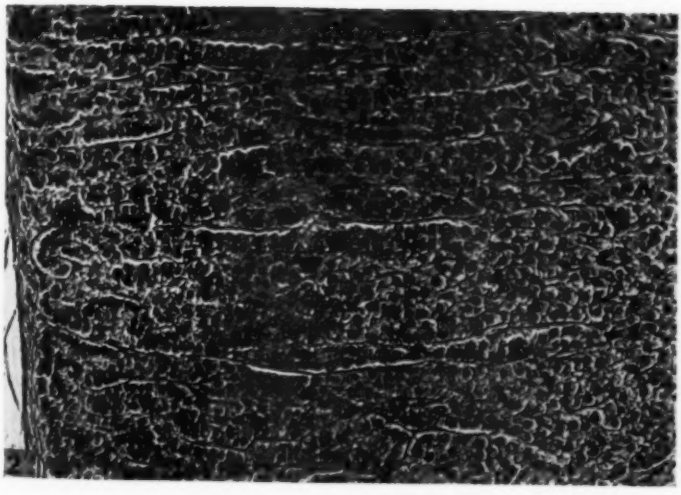
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MYOCARDIAL, HEPATIC AND RENAL DAMAGE RESULTING FROM PARA-AMINOBENZOIC ACID THERAPY

Observations in Human Cases and Experimental Animals

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INTRODUCTION

It now seems well established that para-aminobenzoic (PABA) is a vitamin of the B group, and is necessary for the health of animals, plants and bacteria (1–6). Its biological importance was first recognized in connection with certain pathogenic bacteria through the work of Woods (5), Fildes (6), Selbie (7), and Wood (8) which indicated that the bacterostatic effect of the sulphonamides was exerted by preventing the use of PABA by the bacteria concerned.

War-time studies of rickettsial infections showed that sulphonamide increased the experimental mortality rate in these infections and, because of this, the therapeutic effect of PABA was investigated. Encouraging results, both in the laboratory and clinically were reported (9–19). No record of pathological changes caused by the drug in human subjects has been found, although the pathology of two fatal cases of typhus, treated with it, is said to have been studied (12). Toxic effects following its administration have been obtained experimentally by Scott and Robbins (20), in rats, mice and dogs. They found mice and dogs to be more susceptible than rats. Oral doses of more than 1.0 gm. per kg. would cause death with acute gastroenteritis and alimentary hemorrhage, and doses of 2.0 gm. or more per kg. would cause acute necrosis of the liver.

In the search for a drug to combat rheumatic fever PABA was tried clinically at the Sydenham Hospital, Baltimore, and at the Johns Hopkins Hospital. Dramatic clinical improvement seemed to take place in one case, and for that reason the drug was used, in the maximum doses recommended for rickettsial infections, for rather long periods.

* Commonwealth Fund Fellow, 1946–47.

Two cases of acute rheumatic fever in children were treated with the drug with a fatal outcome. A third case of arthritis, in which the diagnosis was uncertain clinically and at autopsy, was also treated with the drug and died. All presented lesions which are attributed to the drug, and have been reproduced, in a slightly less severe form, experimentally in rabbits. In one of the human cases death can almost certainly be attributed to the drug, while in the other two the drug must have contributed to cause the fatal outcome.

It is understood that the clinical studies of the effects of the drug are to be published separately and only very brief notes on the subject will be given here.

HUMAN CASES

Case 1. A 7 year old white girl was admitted to Sydenham Hospital on August 24, 1946. (Sydenham history number 34406.) She was suffering from an attack of typical rheumatic fever. This was treated with p-aminobenzoic acid which was given along with sodium bicarbonate, the way in which the drug had been used in the treatment of rickettsial infections. The child weighed 28 lbs. and PABA was given every two hours in doses of 2 gms. along with half that amount of bicarbonate of soda. There was marked clinical improvement but the treatment was stopped after a week because red cells were found in the urine on one occasion. Blood levels of over 45 mgm. per cent were obtained. The total amount administered up to that time was approximately 146 gms. After an interval of two weeks a second typical attack of rheumatic fever developed and the PABA treatment was begun again, and again the attack seemed to be suppressed by the drug. This time the amount given was from 1 to 3 grams every two hours, according to the blood levels of PABA. These were estimated daily, and exceeded 45 mgm. per cent on a number of occasions. Sodium bicarbonate was given with the PABA as before. From time to time there was slight nausea, especially following a dose of the PABA, and after the drug had been administered for three weeks nausea and vomiting became marked, the liver was noted to be enlarged, and tender, and the child became febrile. At that time the heart was of normal size and there were signs of mitral insufficiency. The vomiting continued for three days with little relief. Attempts to replace chlorides parenterally caused signs of cardiac failure, and the child developed tetany which had to be treated with calcium chloride on two occasious. During the last 7 hours of life the patient's condition deteriorated steadily with the development of Cheyne-Stokes respiration, and progressive cardiac failure. Attempts at resuscitation with Lanatoside C, oxygen, bronchoscopy, coramine and adrenalin were unsuccessful, and the patient died at 7 a.m. on October 9, 1946. During the final period of PABA therapy a total of approximately 339 gms. were given. The total amount given in the two courses of treatment was about 485 gms.

Autopsy. (Johns Hopkins Hospital Autopsy Number 20197.) Autopsy was carried out on the day of death by one of us (G. W. M.), and the main findings were: Rheumatic heart disease with Aschoff bodies in the myocardium, the left auricle, and mitral valve; and marked deposits of fat in the myocardium, the renal and hepatic epithelial cells (Figs. 1, 2). The fatty infiltration of the heart, kidneys, and liver was believed to be the result of the PABA administration.

Case 2. A 10½ year old white girl was admitted to the Harriet Lane Home of the Johns Hopkins Hospital on July 13, 1946, (History Number A48569). There was a history of rheumatic fever in January, 1946, which had lasted about 6 weeks, and of pain in the chest and shortness of breath in March, 1946. Three days before admission precordial pain, dyspnea and orthopnea had developed. On examination the main findings were those of rheumatic heart disease, with a pulse rate of 140, respiration rate of 28, and blood pressure of 132/70 mm. Hg. There was some respiratory exertion, the heart was enlarged with a rapid rate and sounds of poor quality. There was a generalized precordial systolic murmur and a questionable diastolic murmur at the apex. There was also gallop rhythm. Some rales were noted at the left base posteriorly. The venous pressure was 137 mm. of water, and the circulation time 19 seconds. The vital capacity was 825 cc. On three occasions the sedimentation rate was between 26 and 30 mm. and the throat culture yielded numerous beta streptococci. The electrocardiogram showed myocardial damage. The child weighed 50½ lbs. PABA was administered for a week, July 13–20, in two hourly doses with bicarbonate of soda as in the previous case, and blood levels of about 50 mgm. per cent were obtained. A total of about 148 gms. of PABA was administered. During the first five days in the hospital there was little change in the patient's condition. Then the heart seemed to enlarge, the temperature rose and rales appeared at both bases. Aspirin therapy was begun and the patient was digitalized without improvement. In the last 24 hours there was pulmonary edema which made venesection and sedation with morphine necessary. Oxygen, aminophyllin, and penicillin were administered but the patient died on July 22, 1946, at 6 p.m.

Autopsy. Autopsy was performed on July 23, 1946, at 10 a.m. by Dr. R. D. Sloan (Johns Hopkins Hospital Autopsy Number 20054) and the main findings were: Acute and subacute rheumatic pancarditis, rheumatic pneumonitis, subcutaneous rheumatic nodule, cardiac hypertrophy and dilatation, pulmonary edema and hemorrhage, fatty infiltration of the liver and kidneys, and fatty infiltration of the myocardium (Fig. 3). The fatty infiltration was similar to, but less marked than that in autopsy 20197.

Case 3. A 13 year old white boy was admitted to the Harriet Lane Home of the Johns Hopkins Hospital for the fourth time on June 7, 1946. The history was that at the age of 22 months he had had pneumonia and empyema which had kept him in the hospital 2 or 3 weeks. About 2 weeks after his discharge he was readmitted because of acute arthritis, acute pharyngitis, and cervical adenitis. He

improved and was discharged, but within a few days he was readmitted because of an urticardial rash and joint pains. During this admission his tonsils and adenoids were removed, and following this he was much better. After discharge he had scarlet fever, measles, pertussis and chicken pox. In January, 1945, there was an episode of painful joints and fever and he was followed in the Out-Patient Department with the diagnosis of rheumatic fever, and was treated with aspirin. In July, 1945, he had a recurrence of pain, this time in his muscles. The pain responded to aspirin. About 3½ weeks before his final admission his arms began to ache and he was given aspirin, but next his legs were affected and in spite of increased doses of aspirin he developed a sore throat and fever. All his symptoms became worse and he had a shaking chill 6 days before his final admission. On examination when he was admitted the temperature was 38.2°C, pulse 118, respirations 32, blood pressure 108/60 mm. Hg. He was obviously ill and had a red macular rash on his arms, trunk and legs. There was a systolic murmur and thrill along the left sternal border. The spleen was palpable below the costal margin. There was marked tenderness of the muscles of the upper arms and thighs. The joints were not tender and there was no pain on passive movement. He was anemic with a hemoglobin level of 9 gms. and 3.62 million red cells per cu. mm. Leucocytes were 21,400 per cu. mm., with 79 per cent adult polymorphs, 9 per cent juveniles, 10 per cent lymphocytes and 2 per cent monocytes. He remained anemic throughout his course in hospital despite transfusions and iron therapy. The corrected sedimentation rate was 22 mm. Examination of the urine was negative. Chemical examinations of the blood revealed no abnormality. The throat yielded alpha and beta streptococci. Originally, x-ray examination of the heart, aorta and lungs showed no abnormality. The cerebro-spinal fluid was normal. The patient became steadily worse despite aspirin and penicillin. PABA was begun 3 weeks before death. At this time x-ray showed marked cardiac enlargement and an effusion in the right pleural cavity. The cardiac enlargement was thought to be the result of a pericardial effusion. The PABA was administered from July 19 until July 31, during which time a total amount of 444 gms. was given, in two hourly doses. It was given partially dissolved in 5 per cent bicarbonate solution. The usual dose was 2 gms., or 20 cc. of the 10 per cent PABA suspension in 5 per cent bicarbonate solution. On one occasion a blood level of 110 mgm. per cent was recorded. The PABA seemed to cause a mild remission. About this time two biopsies of the painful muscles were made, but no lesions were found. A morbilliform rash developed 5 days before death. An x-ray examination of the heart and lungs 2 days before death was normal. Generalized clonic convulsions began 12 hours before death and continued until death took place on August 2, 1946. Shortly before death the liver became enlarged, although there was no heart failure. There was also some enlargement of lymph nodes. At the time of death the clinical diagnosis was periarteritis nodosa.

Autopsy. (Johns Hopkins Hospital Autopsy Number 20077.) Autopsy was performed by Dr. B. N. Carle 13½ hours after death. The chief autopsy findings were: non-bacterial organizing pericarditis, extensive splenic and pleural adhesions, splenic enlargement and generalized lymph node enlargement. There were foci of

necrosis in the lymph nodes and spleen. There were a few minute scars in the myocardium, but no Aschoff bodies, no inflammation, and no involvement of the endocardium of the left auricle. There were no vegetations on either surface of the mitral valve. There were small foci of mononuclear cells in the sections of voluntary muscle, and there was hyalinization of some of the voluntary muscle fibers. Some of the renal tubules contained hemoglobin casts and there was associated tubular dilatation. In addition there was sub-acute ulcerative esophagitis, small pulmonary and peri-aortic hemorrhages, and hemorrhage into the bowel. The liver was enlarged (weight 1550 gms.) and was infiltrated with fat (Fig. 4). There were also droplets of fat in the renal epithelium. The myocardium contained fat. The non-bacterial polyserositis, necroses in lymph nodes and spleen, and mononuclear infiltrations in the muscles, together with the arthritis, fever, and cutaneous erruptions strongly suggest one of the collagen-vascular diseases, particularly disseminated lupus erythematosus, but no collagen or vascular alterations were found other than moderate intimal thickening of branches of the coronary arteries. There was no periarterial fibrosis in the spleen and there were no renal glomerular abnormalities.

EXPERIMENTAL STUDY

The marked fatty changes in the heart, liver, and kidneys of the cases described seemed to be an effect of the PABA which all three had received, and attempts were made to reproduce these fatty changes experimentally.

Rats and guinea pigs

The first attempts were unsuccessful. In these experiments dry PABA was fed to a batch of 12 rats and to a batch of 12 guinea pigs, in doses equivalent to those which the children had received, mixed with the pulverized food of the animals (Purina Laboratory Chow). In the case of the guinea pigs, corn syrup was added to the diet to make it more palatable, and small amounts of green vegetables were given in addition. The animals were not kept in separate cages, so the exact amount consumed by each animal was not known. There was a considerable loss of the diet through scattering as the animals ate. When it was found that fatty changes were not being obtained, the amount of the drug given to the remaining guinea pigs was increased to as much as the animals would eat in their diet. This was about 1.5 gm. per day for each guinea pig of about 330 gm. in weight. Although the diet was continued for two months, no fatty livers or kidneys were obtained in the guinea pigs or the rats.

Rabbits

In experiments with rabbits a different method of administration was used. The PABA was partially dissolved in a solution of sodium bicarbonate and was given to the animals by stomach tube. In all the clinical cases sodium bicarbonate had been given along with the PABA and sometimes the two drugs had been given mixed. When 10 gms. of PABA were dissolved in 100 c.c. of 5 per cent solution of sodium bicarbonate, brisk effervescence took place, but a certain amount of PABA remained undissolved. Before a dose was given to the rabbits the mixture was always shaken, but even during administration the drug tended to sediment and to obstruct the orifice of the syringe with which it was injected through the stomach tube. This made it impossible to be sure of the exact amount of the drug that an animal had received. In the experiments to be described the doses quoted are in cubic centimeters of the 10 per cent PABA suspension in 5 per cent sodium bicarbonate solution after shaking. It seemed to be of importance, so far as the production of fatty change was concerned, that the solution should be freshly prepared; for in the case of Rabbit 69 where the mixture had been allowed to stand for a considerable time after preparation, no fatty changes were found, while other rabbits, dosed in the same way with a freshly prepared mixture, showed fatty infiltrations. The usual dose given at a time was 20 c.c.

In all, four experiments, each with a small group of rabbits, were carried out.

Experiment I was carried out as shown in the Table I. All rabbits were albino males and they were fed the routine laboratory diet. In addition, two doses of 20 c.c. each of PABA were given twice during the day, one in the morning, and one in the evening. Rabbit 60 died of having aspirated the morning dose on the second day of the experiment. A frozen section of his liver, stained with Scharlach R and hematoxylin, showed distinct red staining of the cytoplasm of the liver cells in the centers of the lobules without any well defined droplets. A frozen section of the kidney, stained for fat, was exactly like a normal control. In the case of Rabbit 59 the liver, stained for fat, showed small red globules in many of the liver cells. These were distributed irregularly throughout the liver lobules but were more numerous in the central region of the lobules. A paraffin section showed small corre-

sponding vacuoles. The kidney of Rabbit 59, stained for fat, showed vivid red staining of the cytoplasm in the loops of Henle. The convoluted tubules and the collecting tubules were unaffected. In the paraffin section vacuoles, corresponding to the red staining areas, were seen under high power. The heart showed the most marked fatty degeneration of any rabbit studied. The findings in Rabbit 58 seemed to contradict those in Rabbit 59. No fat was found in the heart or liver, and only a few irregularly distributed red staining globules were seen in the loops of Henle in the kidney. As Rabbit 58 had received more PABA than Rabbit 59 it was felt that the presence of fat in the organs of 59 might be due to some incidental effect. It was noted that Rabbit 59 had lost 0.8 kg. in weight during the experiment and, as the effects of emaciation could not be excluded, no conclusion was drawn from this experiment. Another experiment was carried out as follows:

TABLE I

Experiment I

RABBIT NUMBER	ORIGINAL WEIGHT	DURATION OF DOSAGE	TOTAL DOSE	FINAL WEIGHT	FATTY CHANGES
	kg.	*days*	*c.c.*	*kg.*	
58	2.8	10	380	2.6	Heart—0 Liver—0 Kidney—+
59	2.8	9	320	2.0	Heart—++++ Liver—++ Kidney—+++
60	2.5	2	60	2.5	Heart—lost Liver—+ Kidney—0

Experiment II. In this experiment (Table II) PABA in bicarbonate solution was used as in the previous experiment. It was freshly prepared. The stomach tube was passed four times a day and a dose of 20 c.c. was given each time. Rabbit 61 was found dead on the morning of the second day, having received 80 c.c. on the first day. Death was believed to have been due to fluid having entered the lungs during the administration of the last dose the previous night. Frozen section of

the liver revealed droplets, which stained red with Scharlach R, widely distributed throughout the liver. They were less numerous near the portal tracts. Corresponding vacuoles were present in a paraffin section. Fat droplets were also present in the renal epithelium and in the myocardium. Rabbits 62 and 63 both died in the course of the second day of the experiment and again aspiration was thought to be responsible. The liver from Rabbit 62 in a frozen section, contained many red staining globules in almost all parts of the liver lobules. They were numerous in both the central and portal zones of the lobules.

TABLE II

Experiment II

RABBIT NUMBER	ORIGINAL WEIGHT	DURATION OF DOSAGE	TOTAL DOSE	FINAL WEIGHT	FATTY CHANGES
	kg.	*hrs.*	*c.c.*	*kg.*	
61	3.9	12	80	3.9	Heart—+ Liver—++ Kidney—++
62	2.85	26	120	2.85	Heart—++ Liver—+++ Kidney—+++
63	3.5	22	100	3.5	Heart—++ Liver—++++ Kidney—+++

The paraffin section showed marked vacuolation of the liver cells. The kidney, in frozen section, showed fat droplets in the epithelial cells of the convoluted tubules and the loops of Henle. The heart showed definite fatty change. In Rabbit 63 the frozen section of the liver contained many red globules in all parts of the lobules and there were corresponding vacuoles in the paraffin section. In the kidney there were well marked fat deposits of the epithelium of the convoluted tubules. The loops of Henle appeared to be normal. In the paraffin section small vacuoles were seen under high power in the epithelium of the convoluted tubules. The infiltration of fat in the myocardium was again distinct. In this experiment all the animals had died sooner than had been planned and the presence of fat in their organs was an agreeable surprise. There had been no time for weight loss to occur and

the drug seemed to have been responsible for the changes. It was decided to carry out a third experiment with more adequate controls.

Experiment III. In this experiment the rabbits were subjected to a preliminary biopsy of their liver. This was carried out under nembutal and ether anesthesia and, as soon as the animals had recovered from the anesthetic, administration of the PABA-bicarbonate mixture was begun. In the case of Rabbit 69, not included in Table III,

TABLE III

Experiment III

RABBIT	ORIGINAL WEIGHT	PRELIMINARY BIOPSY OF LIVER	DURATION OF DOSAGE	TOTAL DOSE	FINAL WEIGHT	FATTY CHANGES
	kg.			c.c.	kg.	
72	1.85	Only a few droplets	2 days	220	1.7	Heart—+++ Liver—+++ Kidney—++
73	1.85	Occasional droplets	2 days	220	1.65	Heart—++ Liver—++++ Kidney—+++
74	2	Occasional droplets	8 hours	40	2	Heart—+ Liver—+ Kidney—+
75	2.4	Not done	Water 2 days	Water 220	2.5	Heart—0 Liver—0 Kidney—0
76	2	Not done	Untreated 2 days	Anesthetic only	2.1	Heart—0 Liver—0 Kidney—0

the mixture of PABA and bicarbonate had been made for the previous experiment and had stood at room temperature for 19 days. No fatty changes were produced in this animal. In addition to the animals which received the PABA mixture, a control animal was subjected to anesthesia only, and a second control animal received 20 c.c. of water by stomach tube each time a dose of PABA mixture was given to the others. The results are summarized in Table III. In the case of Rabbits 72 and 73 the preliminary biopsies of the livers showed occasional fat droplets in the frozen sections, but these were trivial compared with the

many globules in all parts of the livers after the drug had been given. These latter droplets were most marked in the centers of the lobules but were present everywhere. Marked vacuolation was seen in paraffin sections (Figs. 5, 6). The cytoplasm of the cells of the convoluted tubules and the loops of Henle contained droplets staining with Scharlach R in frozen sections. The hearts in both rabbits showed well marked fatty change (Fig. 7). The control rabbits 75 and 76 showed fatty no changes. Rabbit 74 died after the second dose of the PABA mixture. A frozen section of the liver compared with the preliminary biopsy showed an increase in fat.

DISCUSSION

The presence of fatty infiltrations to such a marked degree in all three human cases which had received the drug seemed to leave little doubt that these lesions were results of the drug. In the experimental animals the fatty changes which were obtained by administration of the drug were somewhat less severe than those in the human cases, but they are regarded as sufficiently marked to establish the relationship. It is not proposed at this time to speculate as to the nature of the process by which these fatty changes are produced by the drug. That problem requires a separate study.

SUMMARY

Two cases of acute rheumatic fever, and one of arthritis of undetermined nature that had received large doses of para-aminobenzoic acid came to autopsy and showed marked to extreme deposits of fat in the epithelial cells of the liver, kidneys and in the myocardium. These lesions were believed to have been caused by the para-aminobenzoic acid, and this was confirmed by the production of fatty changes in the livers, kidneys, and hearts of rabbits to which the drug was administered.

The use of large doses of para-aminobenzoic acid in therapy is not without danger.

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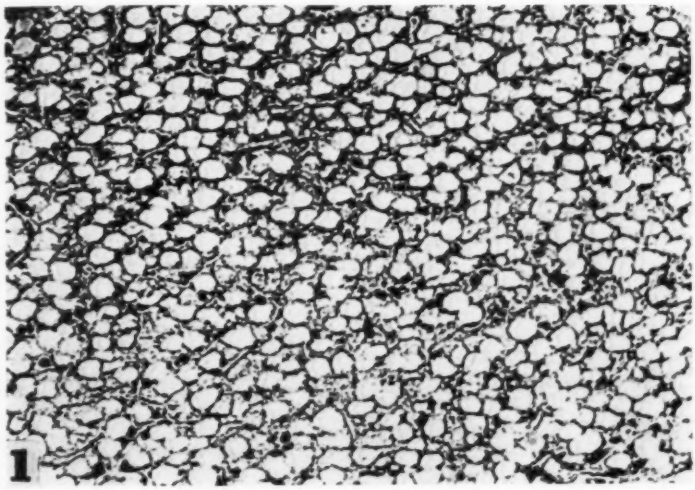
Explanation of Illustrations

(Photographs by Miss Joan Wheaton)

Fig. 1. Liver of Case 1 (autopsy 20197), showing extreme deposits of fat greatly distending the liver cells.

Fig. 2. Kidney of Case 1 (autopsy 20197). There is a very marked deposit of fat in the tubular epithelium. While the outlines of the individual fat droplets are indistinct in the photograph it can be seen that the nuclei are pushed far from the basement membrane toward the free margins of the cells by the fat which stained brilliantly with Scharlach R in frozen sections.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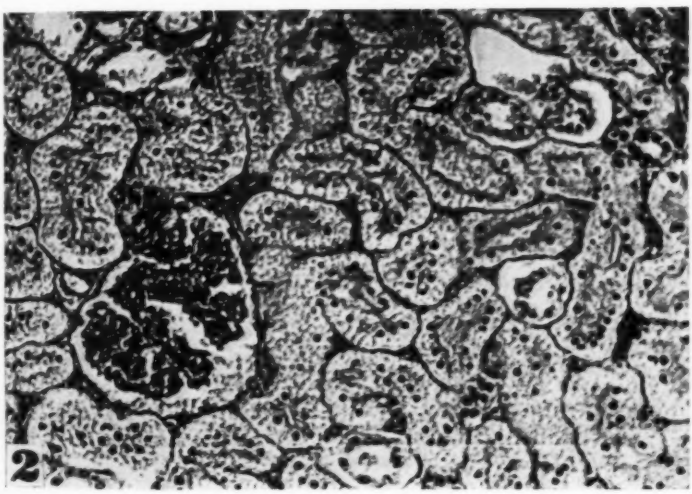
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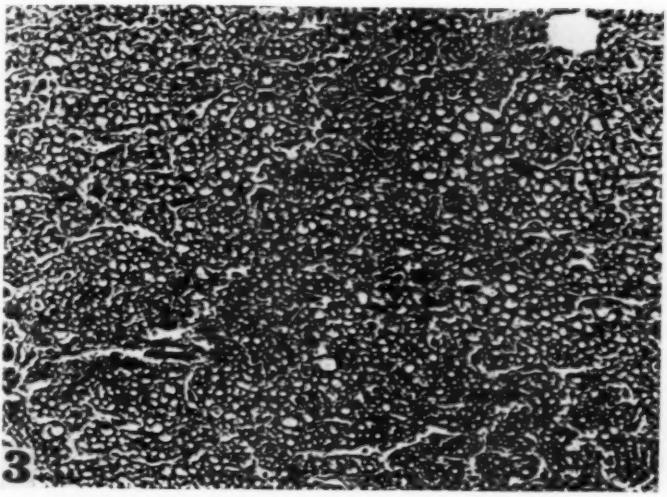
FIG. 3. Liver of Case 2 (autopsy 20054). Marked deposits of fat in the liver cells. Same magnification as Fig. 1.

FIG. 4. Liver of Case 3 (autopsy 20077). Marked deposits of fat in the liver cells. Same magnification as Fig. 1.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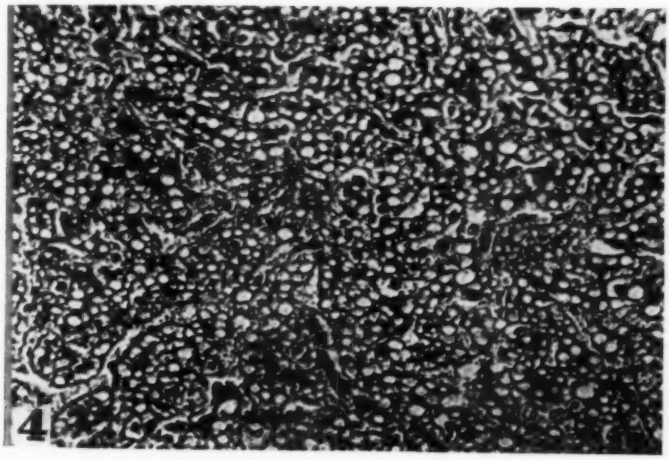
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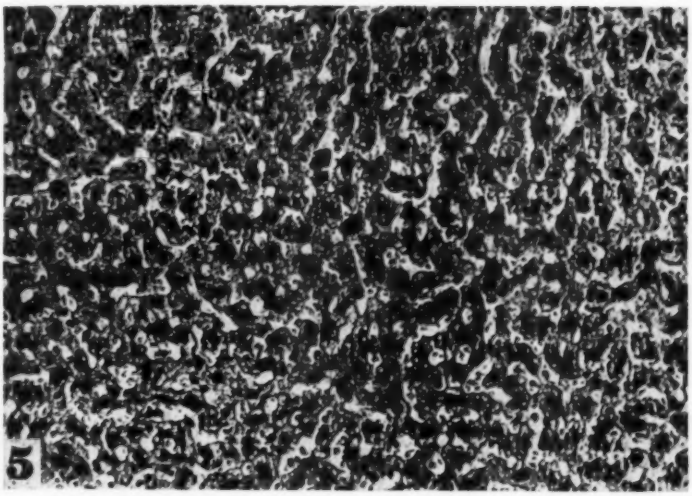
FIG. 5. Biopsy of liver of Rabbit 73 (Experiment III) before administering PABA. There are no fat droplets.

FIG. 6. Liver of Rabbit 73 (Experiment III) at autopsy following administration of PABA. The liver cells contain many fat droplets. Same magnification as Fig. 5.



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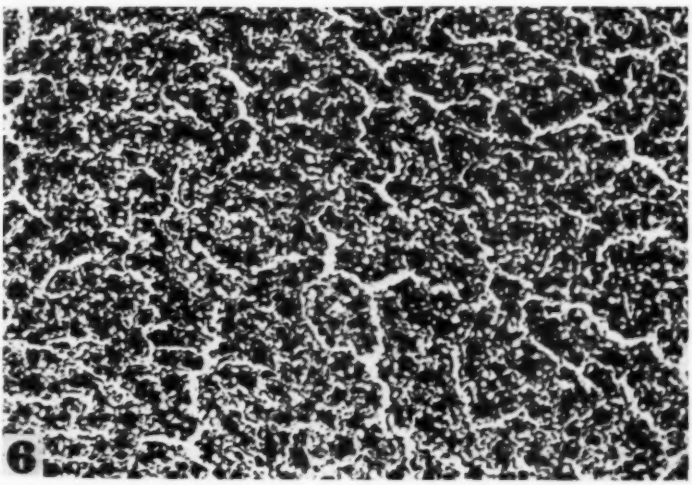

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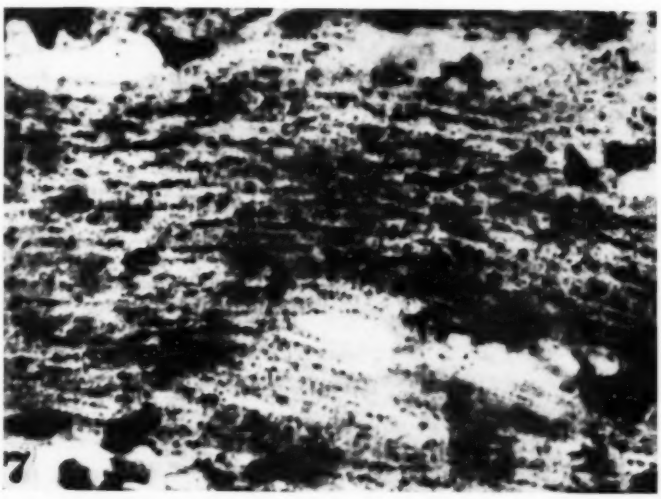
FIG. 7. Heart of Rabbit 72 (Experiment III), stained with Sharlach R. Myriads of fat droplets were present in the myocardial fibers throughout the heart. They appear in the photograph as black dots and lines which lie along the longitudinal striations.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SINGLE VENTRICLE WITH A RUDIMENTARY OUTLET CHAMBER

Case Report

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The condition of a single ventricle with a diminutive outlet chamber while rare, represents a well defined special group which has been carefully described, both from the anatomical and the embryological points of view by Abbott (1), Spitzer (2), and Taussig (3, 4). It is thought to represent an extremely early arrest in cardiac development with the bulbus cordis persisting as a rudimentary outlet chamber. The anterior portion of the bulbus cordis normally becomes the outflow tract of the right ventricle. There is a simultaneous arrest in the development of the ventricular septum so that the primitive common ventricle persists.

The following case report is of interest, not only because of complete diagnostic studies, but also because of its unusual clinical features.

CASE E. R. F. HARRIET LANE HOME OF THE JOHNS HOPKINS HOSPITAL NO. A-61713

This patient, a 17 year old white male, was first seen in the Cardiac Clinic in March 1948 because of dyspnea and cyanosis since the age of thirteen weeks.

Past history

Birth was normal. Cyanosis and dyspnea were first noted at the age of thirteen weeks, concomitant with an attack of pneumonia. Dyspnea and cyanosis were persistent following this illness. His growth and development were delayed. He did not walk until two and a half years of age. He was always small and underweight. His mental development was normal. As he became older, the patient's limitations became more marked so that when he was first seen in the clinic, he was able to walk only one hundred yards before becoming short of breath and fatigued. There was no history of attacks of syncope or paroxysmal dyspnea, nor did he squat when tired. There was an additional symptom of "tender spots" on his legs which had been present for the previous two years.

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Physical examination

Examination revealed a thin, underdeveloped, cyanotic 17 year old boy, dyspneic on the slightest exertion. His heart rate was 100. Blood pressure was 100/80. The heart was enlarged. It extended 2 cm. beyond the mid-clavicular line in the fifth interspace and there was a marked thrust at the apex. A faint, short systolic murmur was present in the fourth interspace just outside the left sternal border. There was also a soft blowing early diastolic murmur in the third interspace at the left sternal border which was only heard after exercise. Examination of the lungs revealed scattered wheezes and fine musical rales. The liver edge was palpable two finger breadths below the right costal margin. The fingers and toes were deeply cyanotic and markedly clubbed. There were tender purpuric areas and many petechiae on both legs.

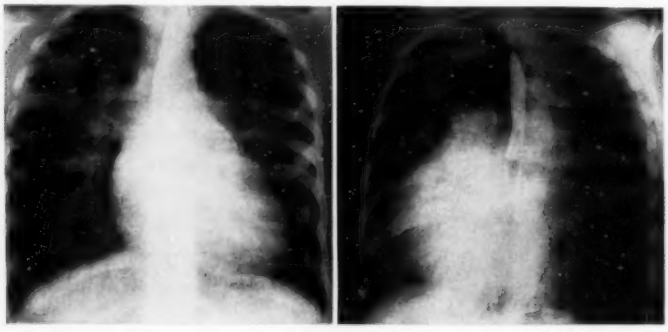

FIG. 1

Laboratory data

Red blood cell count was 10.15 million, hemoglobin 25.2 grams, hematocrit 81.8, white blood cell count 6,000 with a normal differential count. Bleeding and clotting times and platelet count were normal. The arm-to-tongue circulation time, using 4 cc. of Decholin, was 10 seconds.

Fluoroscopic examination

The heart appeared obviously enlarged to the right and left in the anterior-posterior view. The pulmonary conus was concave. There were, however, very large pulsating pulmonary arteries in both hilar regions. In the left anterior oblique position, the right ventricle was markedly enlarged; the left ventricle showed slight enlargement. (See Figure 1)

Electrocardiogram

P waves were high and peaked in lead II. The P-R interval was moderately increased (.19 seconds). In all three standard leads, the QRS complexes were

deflected downward. The precordial leads revealed right ventricular hypertrophy with a high upward deflection of the QRS complex in V_1 and a deep downward deflection of the QRS complex in V_5. (See Figure 2)

Clinical impression

Congenital malformation of the heart, cyanotic group, with markedly increased circulation to the lungs. Complete transposition of the great vessels with a large posteriorly placed pulmonary artery overriding a high septal defect. Because of the patient's desperate condition and obviously poor prognosis and in order to determine whether there was a lesion amenable to surgery, it was decided to do cardiac catheterization and angiocardiography in an effort to establish the diagnosis more accurately.

Because the blood from the femoral artery and right auricle showed essentially the same oxygen content (the samples were not taken simultaneously) and, in

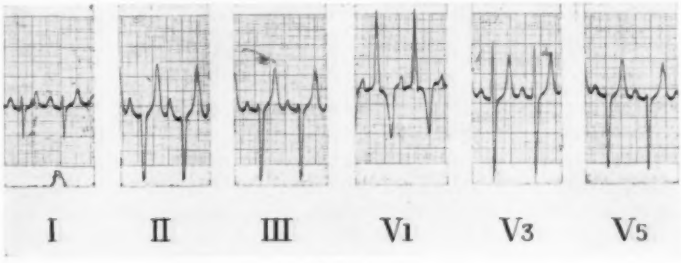

FIG. 2

addition, the content of the pulmonary artery was only 2 volumes per cent below that calculated for the pulmonary veins, it was felt that the basic malformation was a complete transposition of the great vessels. Due to the fact that the pulmonary artery was catheterized, the interpretation was that it overrode a ventricular septal defect and, thus, the clinical diagnosis appeared to be confirmed. Of special interest were the extremely high pulmonary artery flow, and the markedly increased pulmonary artery and right ventricular pressures.

Angiocardiograms (Taken by Dr. Robert Sloan)

The injection was made by way of the right basilic vein and both anterior-posterior and left lateral series were done. The contrast solution entered the heart by way of a moderate sized right-sided superior vena cava, and passed into a large right atrium. The contrast solution appeared to linger in the right side of the heart for an abnormally long time: there was still a considerable concentration of the dye in the region of the right atrium at the end of approximately 8 seconds. In the lateral series at the end of approximately 4 seconds, there was suggestive opacification of the left side of the heart which was believed to indicate the presence of a

septal defect. The aorta was faintly opacified at the end of 3 to 4 seconds, but the degree of concentration of dye within the aorta never became very great. The aorta appeared to arch to the left. In the lateral projection, the aorta appeared to arise fairly far anteriorly. There was no opacification of the pulmonary trunk or of its major branches. There was, however, some slow opacification of the hilar and peripheral parenchymal markings.

Impression

An exact diagnosis could not be made from this examination. The retention of the dye in the right side of the heart and the rather faint opacification of the aorta were contrary to that which would be expected with a complete transposition of the great vessels. The early filling of the aorta suggested either an overriding of the aorta or the filling of the aorta from the left ventricle through a septal defect. Nevertheless, on the assumption that the basic malformation was a complete transposition of the great vessels and that an auricular septal defect would allow a better exchange of oxygenated blood within the heart, the patient was recommended for operation.

Operation

On October 9, 1948, an auricular septal defect was created by Dr. Alfred Blalock using the method previously described by him (6). Following the operation, there was a definite improvement in the patient's condition. He was less cyanotic and dyspneic. He developed a right hemothorax which required tapping on several occasions but, by the fifth postoperative day, he appeared to be doing well. He was comfortable and his color was good with the use of supplementary oxygen. An x-ray, taken at that time, showed a clear left lung and good expansion of the right lung. There was, however, a shadow 1–2 cm. in width which extended along the entire length of the right chest which was thought to represent a pleural effusion. On the seventh postoperative day, following a thoracentesis, the patient developed dyspnea and went into shock. There were physical signs of massive pleural effusion which were confirmed by x-ray. An additional thoracentesis yielded 350 cc. of bright red blood. Despite all efforts, the patient died within ten hours.

Autopsy (No. 21455, Performed by Dr. R. P. O'Donnell)

The pertinent findings were related to the heart and lungs. The heart was moderately enlarged; it weighed 350 grams. The venae cavae entered normally into a large right auricle. The foramen ovale which barely admitted a probe, was functionally closed. Except for a 4 x 0.5 cm slit-like opening produced by the operation, which lay just to the left of the foramen ovale, the auricular septum was intact. The tricuspid valve opened into a large posterior single ventricle and also opened directly into a small, thick-walled, anterior rudimentary outlet chamber which lay in the region normally occupied by the pulmonary conus (see Figure 3). The anterior leaflet of the tricuspid valve was attached to this rudimentary chamber by papillary muscles which arose from its anterior wall; thus part of

the blood from the right auricle was passed directly into the rudimentary outlet chamber. An aorta arose from this rudimentary cavity. The aortic valve showed three normal cusps. The coronary orifices were in the normal position in relation to the aortic valves. A patent ductus arteriosus, 3 mm. in diameter, was present in the usual position. Posteriorly, a large pulmonary artery arose from the common ventricle. The pulmonary valves were thickened and two of the cusps were fused and rather rigid. Atheromatous plaques were present in the artery and its branches; the latter were as large as the aorta. Large pulmonary veins emptied

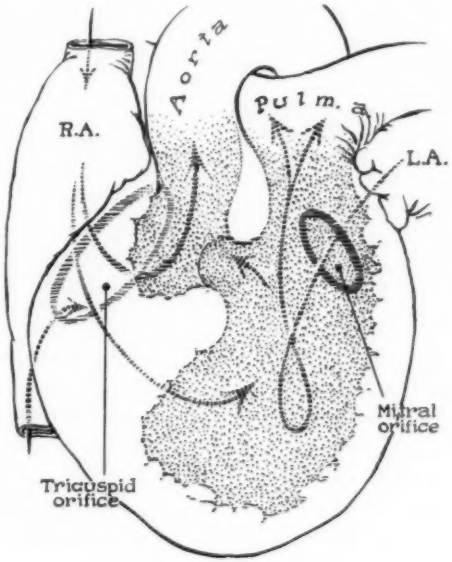

FIG. 3

into a small left auricle which in turn emptied through the mitral valve into the common ventricle.

The right pleural cavity contained about 1200 cc. of clotted blood. The right lung was collapsed and congested. Microscopic sections of the lungs revealed multiple thrombi of the small vessels of the type previously described by Rich in cases of tetralogy of Fallot (7).

Anatomical diagnosis

Single ventricle with a rudimentary outlet chamber; complete transposition of the great vessels, the pulmonary artery arising from the main ventricle and

the aorta from the rudimentary chamber; patent ductus arteriosus; right hemothorax with atelectasis and congestion of the right lung.

DISCUSSION

Despite the failure to make a correct antemortem anatomical diagnosis, the pathological findings readily explained the clinical and laboratory data. First, the anomalous attachment of the tricuspid valve leaflet which directed blood from the right auricle into the diminutive outlet chamber undoubtedly caused a large amount of venous blood to be directed through this chamber into the aorta (see Figure 3). This channeling of blood from the right auricle into the aorta offers an explanation for the marked cyanosis and accounts for the presence of essentially the same concentration of oxygen in the samples of the blood taken from the right auricle and the femoral artery (see Table 1). This is further substantiated by the early faint appearance of dye in the aorta as well as the anterior position of the aorta noted in the angiocardiograms. Also, it makes apparent the reason for the clinical improvement manifested by the patient following the creation of an auricular septal defect; i.e., the admixture of arterial and venous blood in the auricles caused a larger amount of oxygenated blood to be directed to the systemic circulation and similarly a larger amount of unoxygenated blood was directed to the lungs.

Secondly, the presence of a large single ventricle receiving blood from both auricles, probably prevented a sufficient concentration of diodrast from entering the pulmonary artery at any one moment for opacification of this vessel due to a dilution of the dye in the ventricle by large amounts of arterial blood entering from the left auricle. The marked difference of 7.6 volumes per cent oxygen content between the right auricle and the "right ventricle" (see Table 1) is in accord with the findings reported by Bing to be indicative of a single ventricle (8).

Thirdly, the origin of a huge pulmonary artery from the single ventricle explains the markedly increased pulmonary flow, as indicated by calculation, using the Fick principle (see Table 1); this finding also explains the fluoroscopic evidence of bilateral large pulsating pulmonary arteries. That the pulmonary artery received largely arterial blood is indicated by the extremely small "effective" pulmonary flow reported by Dr. Bing and his associates (5).

The original clinical diagnosis of complete transposition of the great

vessels with a large posteriorly placed pulmonary artery overriding a septal defect was in a physiological sense confirmed. As in a classical transposition with the aorta arising from the right ventricle, in this case almost pure venous blood was directed into the aorta. Also, a large posteriorly placed pulmonary artery was present through which both venous and arterial blood was ejected.

Taussig (3, 4) has carefully analyzed and discussed the typical clinical and roentgenological findings to be expected in a single ventricle with diminutive outlet chamber of the type in which there is transposition of the great vessels. In two respects, this case differs from her description; the apparent enlargement of the right ventricle in the left anterior oblique position and the presence of marked cyanosis. For the first, we have no adequate explanation except the age of the patient. The cyanosis, as explained above, was due to the accompanying anomalous position and attachment of the tricuspid valve. It is interesting to note that, in the case reported by Glendy, Glendy and White (9), with the same basic malformation in which the tricuspid valve was normally placed the child became cyanotic only when swimming and just before death.

SUMMARY

A case of a single ventricle with a rudimentary outlet chamber, complicated by an anomalous tricuspid valve and transposition of the great vessels is reported. The relation between the anatomical findings and the clinical features and the data obtained from cardiac catheterization and angiocardiography is discussed.

The patient appeared to be temporarily benefited by the surgical creation of an auricular septal defect. Death was probably caused by a massive hemothorax.

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A PECULIAR PNEUMONIA ASSOCIATED WITH RETINAL CYTOID BODIES*

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INTRODUCTION

Three patients having a peculiar pneumonia associated with retinal cytoid bodies were observed at the Johns Hopkins Hospital within the period October, 1947, to January, 1950. The clinical and pathological manifestations of this illness, the cause of which is unknown, will be described.

This illness, varying from three to six months in duration, was characterized by fever, increasing dyspnea with signs of diffuse pneumonitis, and the presence of numerous cytoid bodies in the retinae. Terminally, severe dyspnea, cyanosis and tachycardia developed which were out of proportion to the physical signs of pulmonary involvement. Serial x-rays of the chest showed extensive and progressive alteration.

The histological changes were similar in each case and were characterized by: (1). The presence of thick, eosinophilic, hyaline membranes lining the walls of many alveoli; (2). Edema fluid and frequently hemorrhages filling many alveoli, inflammatory cells being sparse; (3). Extensive organization of the alveolar exudate by recently formed connective tissue, and (4). The extension of metaplastic bronchiolar epithelium into neighboring areas. In each case typical cytoid bodies were found in the nerve fiber layer of the retina.

PRESENTATION OF CASES

Case I. J. N. (J. H. H. 434348). This 35 year old negro janitor visited the Dermatology Clinic of the Johns Hopkins Hospital on September 2, 1947, because of a "breaking out" on his scalp, face, extremities and trunk of four weeks' duration. A similar eruption in 1945 had been called psoriasis. His general health had been excellent, and the only other illnesses he recalled were syphilis in 1944, treated with arsenic, bismuth and penicillin, and a gonorrheal infection acquired in

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1937 and again in 1944. Biopsy of the skin confirmed the diagnosis of psoriasis and local treatment was instituted. The patient also stated during a medical examination one week later that during the past six months he had lost 16 pounds in weight and that for two weeks he had been having migratory joint pains. These pains were only moderately severe but persistent. They had not been associated with local swelling, redness or heat. In addition, during this period, he had noted for the first time mild dyspnea on exertion which was growing more marked. There was no associated cough or other indication of a respiratory infection. His appetite had become poor, and he was not sleeping well. On September 15, 1947, he was admitted to the hospital.

Physical Examination on Admission: Temperature 100.6° (rectal), pulse 84, respiration 18, blood pressure 124/80. He was well developed, well nourished, appearing acutely but not seriously ill. Numerous psoriatic lesions were present on his forehead, scalp, face, chest and abdomen, arms and legs. These varied in size and had discrete scalloped edges with slight elevation and scaling in the center. A general glandular enlargement was noted with particular prominence of the posterior cervical and inguinal lymph nodes. The initial funduscopic examination was normal. Expansion of the chest was poor but symmetrical. There was dullness at both bases posteriorly with bronchial breath sounds, coarse, crackling rales and increased transmission of the spoken and whispered voice. A pleural friction rub was heard at the left base. The heart was normal in size, and the rhythm was regular. A soft, systolic murmur was audible at the apex and base. The abdominal findings were normal. There were no neurological alterations. Although the patient complained of arthralgia, there were no objective changes in the joints.

Admission Laboratory Examinations: The urine had a specific gravity of 1.016. There was no sugar or albumin, and the microscopic examination was normal. The red blood cell count was 4,130,000, and the hemoglobin 13 grams. The hematocrit was 35 per cent. The cell indices were normal. The sedimentation rate was 30 (corrected). The icterus index was 7. The white blood cell count was 6,740 with a normal differential. The serological test for syphilis was negative. The total serum protein was 6.4 grams with 3.6 grams albumin and 2.8 grams per cent globulin.

X-ray of the chest showed that both lung fields contained focal mottled lesions thought to be compatible with some unusual form of pneumonitis.

Course in the Hospital: He died 3 weeks after admission. His course was persistently febrile, the temperature fluctuating between 100–101°. He continued to complain of painful joints, although objective changes were never observed. Aspirin produced some relief of pain and transient defervesence. As time went on he became progressively more dyspneic and developed a moderately productive cough. As the dyspena became accentuated, the temperature, pulse and respiratory rates increased. Physical signs of pneumonia became more pronounced at the lung bases. X-ray of the chest revealed multiple small areas of pneumonitis scattered throughout both lung fields. Two weeks after admission cytoid bodies were first noted in the fundi, and later fresh hemorrhages were also seen. Penicillin, streptomycin and

sulfadiazine were given without effect. Just prior to death, dyspnea became intense. Temperature rose to 104°, and there was an excessive tachycardia. The abnormal findings on physical examination of the lungs did not seem adequate to account for this greatly exaggerated respiratory distress. The patient became very apprehensive. He had a generalized convulsion and died 27 weeks after the onset of his illness.

Additional Studies: Numerous blood cultures were sterile. Tests were repeatedly negative for cold, tularemia, brucella and heterophile agglutinins. The agglutinin titre for streptococcus MG which was 1+ at a dilution of 1/20 on September 19, rose to 1+ at a dilution of 1/80 on October 1. Only alpha streptococcus, neisseria and staphylococcus were isolated from the sputum. Studies of gastric washings and sputum showed no tubercle bacilli. He was tuberculin negative at dilution 1–1000. The histoplasmin skin test was also negative. Several electrocardiograms revealed lowering of the T waves in the limb leads and in CF-5. A lymph node biopsy disclosed only lymphoid hyperplasia. He was seen by an ophthalmological consultant who described several small white fluffy exudates in both fundi which were considered to be typical cytoid bodies. The vessels were not remarkable.

Autopsy Examination: (No. 20835). The skin was seen to be covered by discrete patches of a scaly, erythematous, psoriatic eruption. The superficial lymph nodes were enlarged. About 75 cc. of clear fluid was found in the right pleural cavity. The pleural surfaces were smooth. The lungs felt heavy, rubbery and nodular. When cut these nodules were found to be large, irregular, grey areas of consolidation, which were confluent throughout the left lung. Some of these areas were hemorrhagic in color. No edema was noted. The bronchial mucosa was red and edematous. The bronchial and tracheal lymph nodes were enlarged. The heart weighed only 380 grams, but the right ventricular myocardium measured 6 mm. in thickness and was thought to be hypertrophied.

Microscopically, the major lesions were found in the lungs where all sections showed marked alterations. In extensive areas, pulmonary alveoli and atria had thick eosinophilic hyaline membranes lining their walls (Figure 1). In these regions there was pulmonary edema and frequent intra-alveolar hemorrhage. Large mononuclear and sometimes multi-nuclear cells were occasionally seen lying beneath the hyaline membranes. These were very prominent where the changes were older and organization had begun. Mononuclear cells, chiefly lymphocytes and plasma cells, were found in the alveolar exudate and in the slightly thickened and edematous alveolar walls. Rarely, masses of macrophages were encountered in the alveoli. Generally, the exudate contained but a few cells, and only occasional polymorphonuclear cells were seen. There was widespread organization of the alveolar exudates, alveolar lumina being completely plugged by a recently formed, collagen poor, cellular connective tissue (Figure 2). These fibrous masses distorted the alveoli only slightly, though they often passed through greatly enlarged pores of Cohn to be continuous with similar masses. The bronchioles were largely free of luminal or intramural exudate, but a few showed hyperplasia and metaplasia of the

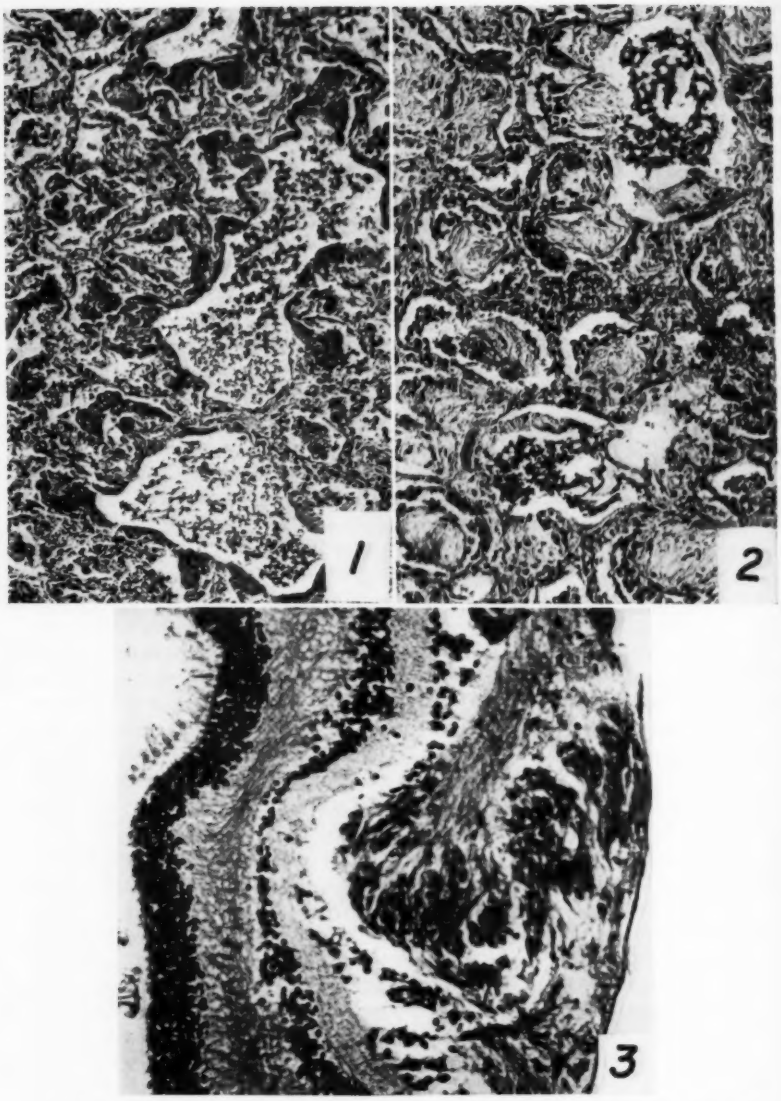


FIGURE 1. (No. 20835). The densely stained hyaline membranes lining air spaces and associated with pulmonary edema are shown. The sparse cellular exudate is apparent.

FIGURE 2. (No. 20835). The extensive collagen-poor connective tissue organization of the alveolar exudate is shown. Remnants of hyaline membranes may be seen as well as edema.

FIGURE 3. (No. 20835). Showing small globular and elongated cell-like bodies in the nerve fiber layer of the retina.

epithelium. Islands of this metaplastic epithelium had frequently extended out into the adjacent air spaces and were sometimes found lying in the organized or organizing exudate. Unfortunately, the available sections showed few larger bronchioles or bronchi. The pleura was normal. No inclusion bodies were found in the epithelial cells. Bacterial stains were negative.

The retina showed normal vessels, a very slight suggestion of papilledema and several cytoid bodies. These were in the nerve fiber layer and consisted of small globular and elongated eosinophilic bodies, approximately 8 micra in diameter but often much longer (Figure 3). Some of the more elongated masses appeared to be greatly swollen fibers continuous with those of the nerve fiber layer. No nuclear material was seen in any of these bodies. The lymph nodes were hyperplastic. The sections of other viscera including the vessels, heart, spleen and kidneys were normal.

Case II. M. F. S. (J.H.H. 439395). This 55 year old negro housewife entered the hospital because of fever, shortness of breath and headache. Her general health had been excellent but for the usual diseases of childhood. Two years before admission she had a febrile illness accompanied by cough and chilly sensations lasting for 2 weeks which was said to be pneumonia. Four months prior to admission a dry, scaling eruption had appeared on her arms, spreading to her thorax and face.

Six weeks prior to admission she had developed a steady, dull, frontal headache which continued unabated. Shortly after the onset of the headache, she had two shaking chills after which she continued to feel feverish. A nasal discharge began, and she had several epistaxes. She then developed a cough productive of 3–4 tablespoons of thin, white sputum daily. There was anorexia with loss of weight. A week before entry slight exertional dyspnea was noted, and she felt more comfortable with the head of the bed elevated. Finally, she began to have pleuritic pain in both chests. The cough, dyspnea, and fever continued, and she was admitted on October 17, 1947.

Physical Examination on Admission: Temperature 102.8° (rectal), pulse 110, respiration 26, blood pressure 124/78. The patient was very obese and appeared chronically as well as acutely ill. She was short of breath lying flat. There was some seborrheic dermatitis of the scalp and about the ears posteriorly. A rough, scaling eruption was present over the bridge of the nose and the cheeks and over the extensor surface of the extremities. Over the chest there was a rather marked hyperpigmentation and a few scaly lesions. There was bilateral congenital shortening of each fourth metacarpal bone. The retinal arteries showed slight narrowing. There were numerous superficial exudates in both retinae and a few flame-shaped hemorrhages. The teeth were in very poor condition. The tonsils were enlarged. The pharynx was moderately injected. Numerous medium moist rales were heard over the lower portion of both lung fields. A faint systolic murmur was heard at the base of the heart. The liver and spleen were not palpable. The reflexes were physiological. There was no glandular enlargement.

Admission Laboratory Examinations: The urine had a specific gravity of 1.012.

There was no sugar and only a trace of albumin. The sediment was not unusual. The white blood cell count was 5,300 with 23 per cent juveniles, 50 per cent polymorphonuclears, 5 per cent eosinophiles, 16 per cent lymphocytes and 6 per cent monocytes. The red blood cell count was 5,230,000, hemoglobin 11.2 grams and hematocrit 38 per cent. The sedimentation rate was 42 (corrected). Platelets were normal, and there was no sickling. The serological test for syphilis was positive with a titre of one unit. No blood, parasites or ova were found in the stool.

Course in the Hospital: She remained in the hospital for 8 weeks until her death. During this period she continued to have a fever with diurnal swings from 100° to 103°F. Later, this became associated with an excessive tachycardia. Dyspnea gradually increased. She continued to have a severe, non-productive cough. Rales persisted in the lower half of both lungs. X-ray of the chest on the 21st day of October revealed diffuse, soft appearing non-specific linear infiltration throughout both lung fields, more marked on the right (Figure 4). Subsequent films disclosed spread of the process with confluence of the mottled infiltrates (Figure 5). She was given large doses of penicillin without effect. Gradually dullness on percussion spread over the lung bases, more marked on the left. The patient grew more drowsy, and during early December complained of pain on motion of both knees. Although the left knee was tender to palpation, there was no demonstrable swelling. She became progressively more dyspneic. During the latter part of October she developed some hoarseness following a sore throat. There was no evidence of tonsillitis or pharyngitis at this time, but the epiglottis showed an area of redness along the free margin, and the posterior ends of both vocal cords were injected. The pulse rate had been very rapid, but on December 8 it suddenly fell from 120 to 80. She was found to have numerous extrasystoles which were nodal in origin. Her condition became increasingly critical. She was disoriented and combative and very cyanotic. She died on December 10, fourteen weeks after onset of her illness.

Additional Studies: The serum non-protein nitrogen was 21 mgm. per cent, fasting blood sugar 107 mgm. per cent, blood calcium 9.9 mgm. per cent, total serum proteins 6.6 gm. per cent, with albumin 3.1 grams per cent and globulin 3.5 grams per cent. Alpha streptococcus, staphylococcus albus and a few pneumococci were cultured from the sputum. Numerous blood cultures were sterile as were cultures of the urine. Sputum examinations and gastric washings were negative for tubercle bacilli. Agglutinations for typhoid, paratyphoid, proteus, brucella were negative, and cold agglutinins were not demonstrable. Streptococcus MG agglutinations were positive in a dilution of 1–160 on October 18. On October 31 the titre was 1–320, and on November 12 it was 1–640. By November 20 the titre had fallen to 1–80. Serum taken about 69 days after onset of illness was negative for complement fixing antibodies of Q fever, psittacosis, lymphogranuloma venereum and lymphocytic choriomeningitis. Tuberculin and histoplasmin skin tests were negative. Lumbar puncture was normal. The venous pressure was normal as was the circulation time. Electrocardiogram taken October 18 showed a rate of 107 with a normal sinus rhythm. There was slight left axis deviation. T-1 and T-2 were flat. An oph-

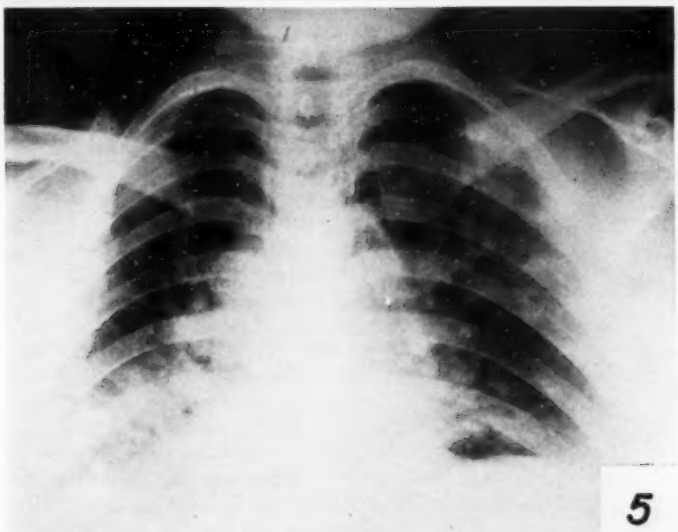


FIGURE 4. X-ray of the chest of patient M. S., taken October 20, 1947, showing soft, non-fibroid poorly demarcated patches of infiltration alternating with strands of infiltration which appear to be distributed along the bronchovascular markings.

FIGURE 5. X-ray of the chest of patient M. S., taken November 14, 1947, showing progression of the soft infiltration with confluent areas.

thalmological consultant considered the cotton fluff exudates to be typical cytoid bodies (Figure 6).

Bone marrow biopsy revealed a considerable increase in the number of eosinophiles. A section of striated muscle was normal. An axillary lymph node showed marked hyperplasia of the lymphoid follicles.

Autopsy Examination: (*No. 20957*). The pleural and pericardial surfaces were smooth. The heart was slightly enlarged and dilated. The lungs were very heavy, and on section showed confluent areas of grey consolidation, patches of hemorrhagic discoloration and what seemed to be atelectasis. The lungs were involved almost completely, only small areas of pink air-containing tissue remaining. The bronchial mucosa was reddened. Fat necroses were seen in the pancreas. The spleen, kidneys and brain as well as other organs showed no macroscopic lesions.

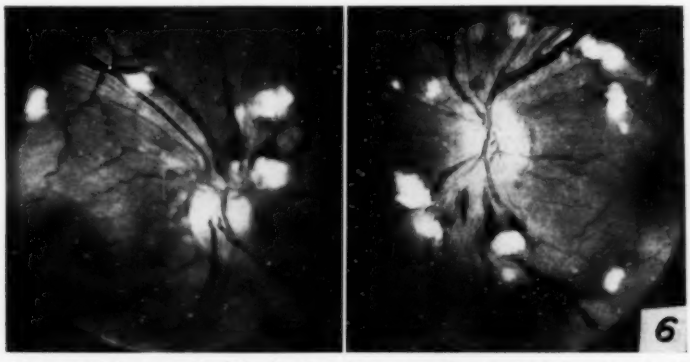


FIGURE 6. Photograph of the fundus of the eyes of patient M. S. taken October 25, 1947, showing typical cytoid bodies and also small hemorrhages.

Microscopically: All portions of the lungs were markedly altered. Pulmonary edema filled the alveoli and atria of large areas. A very deeply eosinophilic hyaline membrane lined the walls of many air spaces (Figure 8). In such areas, large elongated cells, usually mononuclear but sometimes multinucleated, often lay beneath the membrane. Hemorrhages into alveoli were very prominent in a few regions. An occasional bronchiole showed replacement of the surface mucosa by chronic granulation tissue and their walls were infiltrated by round cells. No fresh ulcerations were seen. Squamous metaplasia of bronchial epithelium was frequently present and had grown out into adjacent air spaces where it was seen as small islands in the organizing and organized exudate (Figures 9 and 10). Several small bronchi had polymorphonuclear cells in their lumina and a very few foci of acute lobular pneumonia were found suggestive of a secondary bacterial infection. Several fresh pulmonary arterial thrombi were present which showed no organization. Sections of the retina disclosed an eosinophilic mass in the nerve fiber layer distorting other

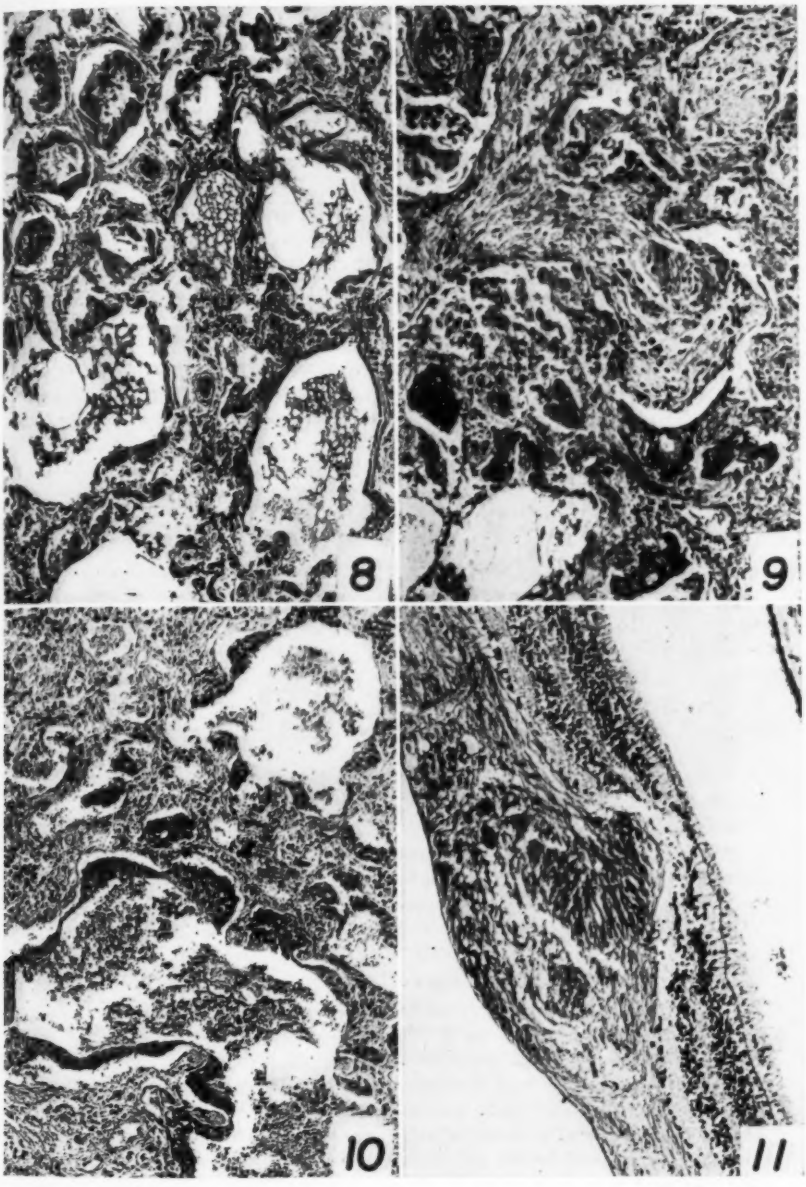


FIGURE 8. (No. 20957). The hyaline membranes and pulmonary edema with scanty cellular exudate are seen.

FIGURE 9. (No. 20957). Organized and organizing alveolar exudate is seen with small nests of metaplastic bronchiolar epithelium.

FIGURE 10. (No. 20957). The prominent squamous metaplasia of bronchiolar epithelium, here lining air spaces, is shown.

FIGURE 11. (No. 20957). Typical retinal cytoid bodies are seen in this nerve fiber layer lesion.

retinal layers and somewhat resembling an exudate. Globular hyaline bodies typical of the so-called cytoid bodies were seen (Figure 11). No cellular exudate, vascular lesions or hemorrhages were elsewhere present. No papilloedema was evident. The liver showed marked fatty infiltration of the cells. In a bronchial lymph node, caseous and hyaline tubercles were seen.

Case III. L. H. (J.H.H. 521267). This 64 year old white housewife was admitted to this hospital for the first time on November 18, 1949, complaining of weakness, loss of weight, fever, cough and mild exertional dyspnea. During her youth she had mild bronchial asthma. In December, 1948, the patient had an illness called "influenza," lasting for several days and followed by diarrhea which persisted for two months. Whether this episode is pertinent to the present illness is not clear, for she felt relatively well after the subsidence of the diarrhea until August 1, 1949. At that time she once again had a febrile illness, said to have been influenza, characterized by coryza, sore throat, myalgia, headache and cough. After ten days the acute symptoms subsided, and she again became active but continued to have a low grade fever, mild malaise, headache and a cough. The cough persisted until the time of admission. It was dry, hacking, occurring in exhausting paroxysms, at times lasting an hour and frequently occurring at night. She had a poor appetite and began to lose weight. Seven weeks prior to admission she was studied at another clinic where it was noted that her temperature was 100.5° (oral). There was some hyperemia of the nasal mucosa with a moderate amount of mucopurulent exudate. Several small glistening exudates were seen in the central portion of the right fundus. Tachycardia was noted, but the heart and lungs were otherwise described as normal. The liver was slightly enlarged. She was admitted to a hospital and treated with penicillin, streptomucin, aureomycin and chloramphenicol without altering the course of her illness. She was then sent to this hospital for observation.

Physical Examination on Admission: Temperature, 99.6°; pulse rate 100; respiratory rate 20; blood pressure 120/65. She appeared chronically ill, coughing frequently, producing yellowish sputum. There was evidence of recent weight loss. The skin and mucous membranes were clear. No glandular enlargement. Funduscopic examination revealed numerous cytoid bodies in each fundus (Figure 7). There was a mild degree of emphysema. The right diaphragm descended poorly. Fine moist rales persisting after cough were heard at both lung bases, particularly the left. There was a soft basilar systolic murmur. Otherwise, the heart was normal. The liver and spleen were not palpable. The neurological system was not unusual.

Admission Laboratory Studies: The urine had a specific gravity of 1.012. It contained no sugar or albumin, and the sediment was normal. The red blood cell count was 5 million, the hemoglobin 14 grams. The sedimentation rate was 34 (corrected). The cell indices were normal. The white blood count was 9,750 with 8 per cent juveniles, 49 per cent polymorphonuclears, 7 per cent eosinophiles, 29 per cent lymphocytes and 5 per cent monocytes. The serological test for syphilis was negative. The stools were guaiac negative and contained no ova or parasites. The blood chemical findings were: Non-protein nitrogen 24 mgm. per cent, CO-2 27.6 meq.,

chlorides 100.3 mgm., total protein 6.8 gms. per cent, albumin 3.0 gm., globulin 3.8 gms. per cent, cholesterol 314 mgm. and bilirubin 0.8 mgm. X-ray of the chest showed soft, linear infiltration scattered diffusely through the left base. The right lung was moderately involved by a similar infiltrate.

Course in the Hospital: Her temperature was persistently elevated between 100° and 101°F with an associated tachycardia which was somewhat excessive. Paroxysms of dry, hacking cough continued. She complained of weakness, general malaise, and vague musculo-skeletal aching. She was mildly dyspneic when she got out of bed. Physical examination of the chest revealed abnormalities which varied in extent and location from week to week. On December 8 a bronchogram was done and was normal. Four days later her temperature was 101.2°F (oral), she had generalized aching and complained that her chest felt tight, as though she had asthma.

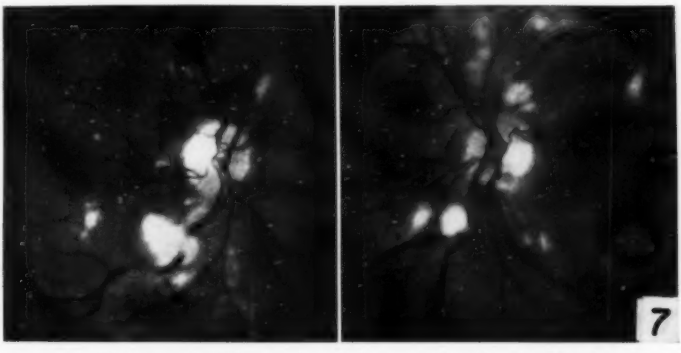


FIGURE 7. Photograph of the fundus of the eyes of patient L. H. taken January 6, 1950, showing typical cytoid bodies.

The elevation in temperature continued for several days, and a papular eruption appeared over the bridge of her nose and forehead. Her dyspnea increased. It was thought she had a reaction to iodine. She was allowed to go home over Christmas, to return on December 30 for therapy with adrenocorticotropic hormone, the provisional diagnosis at that time being disseminated lupus erythematosus. Upon returning the low grade fever persisted, and she was more dyspneic. In walking across the room her respirations increased from 26 to 40 per minute, and the pulse rose to 140. X-ray of the chest on December 30 showed more widespread infiltration at both bases, and an effusion in the left midlung region (Figure 12).

On January 6, ACTH therapy was begun, and within 48 hours she began to improve. Her temperature became normal: her cough cleared, and the rales were no longer audible. Her exercise tolerance increased as did her appetite, and she gained weight. The sedimentation rate fell to normal. By January 18 she was walking about freely without dyspnea and felt quite well. She was receiving 20 mgm. ACTH each

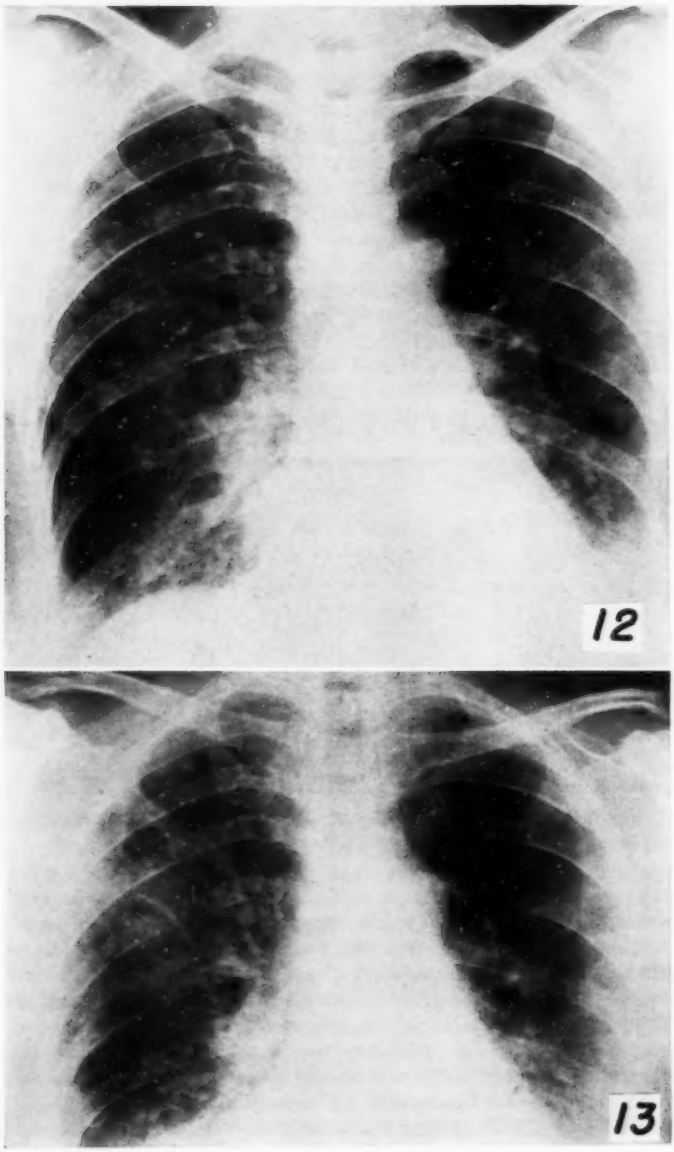


FIGURE 12. X-ray of chest of patient J. H. taken December 30, 1949, showing diffuse infiltration at the left base. The right lung shows a moderate amount of diffuse, soft infiltration which is arranged in linear fashion in several areas.

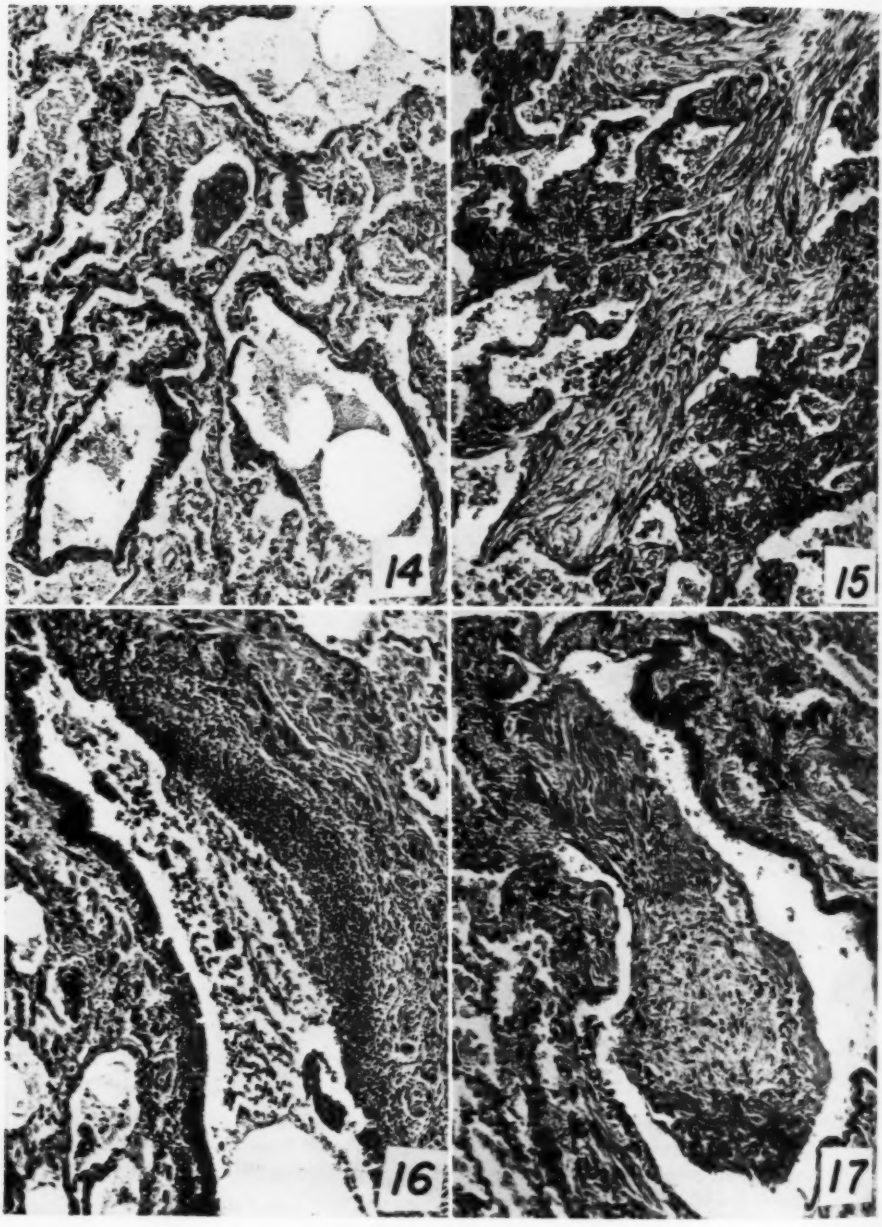
FIGURE 13. X-ray of chest of patient J. H. taken January 23, 1950, showing extension of the soft infiltrative process throughout both lung fields.

day. However, she had become edematous and had a keratotic acne about the shoulders. A few basilar rales were heard, and there was a slight rise in temperature in the evening. ACTH was discontinued on January 20, at which time her acne had increased and she was quite water-logged. At first it was thought that she was having the rebound phenomenon seen so often in patients with lupus erythematosus as treatment with ACTH is tapered, and which usually subsides spontaneously. By January 25, however, her condition was so critical that in spite of the fact that she had not lost her edema, ACTH was resumed. At that time there were numerous fine rales throughout both lung fields (Figure 13). Dyspnea was progressive as was cyanosis. Her temperature promptly returned to normal, but her pulse rate rose to 160. She became more tachypneic. The rales had cleared for the most part, but the breath sounds were tubular in character over both lungs. She became more cyanotic and died from progressive pulmonary insufficiency on January 29, 24 weeks after onset of illness. Just before death 400 ccs. of straw-colored fluid were removed from the right pleural cavity.

Additional Studies: No pathogenic bacteria were cultured from the sputum. Several blood cultures were sterile. The psittacosis complement fixation reaction was negative. Agglutination reactions for Brucella, streptococcus MG and heterophile antibodies were negative. The white blood cell count remained normal but for occasional mild transient elevations when receiving ACTH. She did not develop anemia. The urine was constantly clear. On admission the electrocardiogram showed only left axis deviation. As the illness progressed there was lowering of the T waves. An ophthalmological consultant described typical cytoid bodies in both fundi, the vessels being normal.

Autopsy Examination: (*22206*). Several hundred cubic centimeters of clear, straw-colored fluid were present in each pleural cavity, and a few thin fibrous adhesions were found on the right. The heart was neither enlarged nor dilated, and the valves were normal. Moderate coronary arteriosclerosis was present. The pleural surfaces of the lungs were opaque and granular. The lungs were heavy, together weighing 1400 grams. The major bronchi contained much dark brown mucus. The cut surfaces showed areas of hemorrhagic edema, patches of firm, dry, grey-red consolidation and depressed areas of rubbery glistening tissue in which the lung markings were indistinct. Foci of emphysema were evident. The adrenals, carefully trimmed of adjacent tissue, weighed 7.8 on the right and 7.2 grams on the left.

Microscopically, the lesions of greatest interest were in the lungs. Eosinophilic hyaline membranes lined atrial and alveolar walls (Figure 14). Occasional polymorphonuclear cells, but for the most part a moderate mononuclear cell exudate accompanied this membrane formation. In rare foci polymorphonuclear cells accumulated about necrotic alveolar walls. Numerous alveoli were filled with foam cells, located for the most part where there were few or no hyaline membranes. There were fresh hemorrhages in many alveoli, with formation of fibrin masses filling the alveoli. Such fibrin masses seemed distinct from the hyaline membranes. In some areas, no cellular exudate was found, the alveoli being filled with edema



FIGS. 14–17

coagulum. In the involved areas the alveolar walls generally showed interstitial edema and mononuclear cell infiltration. These cells were predominately lymphocytes but some were plasma cells and macrophages. In many regions early organization of the hyaline membranes and of the alveolar fibrinous exudate was prominent. Still other areas showed complete fibrous organization of the alveoli which were filled with connective tissue plugs, without great distortion of the general pulmonary architecture (Figure 15). Several large bronchioles had polymorphonuclear cells beneath the mucosa with squamous metaplasia of the mucosa. There was acute ulceration of the mucosal surface of some bronchioles with extension of polymorphonuclear cells through the wall beneath the ulcer (Figure 16). Many contained plugs of organizing exudate which were attached to the walls along portions where the mucosa was denuded (Figure 17). In many areas there was metaplasia of the epithelium of the bronchioles with partial plugging of their lumina and extension of the epithelium into the adjoining air spaces and alveoli, until occasionally these too were filled with epithelial cells (Figure 18). An occasional bronchus possessed a slightly thickened hyaline basement membrane but no eosinophiles were seen. Bacterial stains were negative.

The adrenal cortex revealed a normal zona glomerulosa. The cells of the fasciculata were depleted of normal amounts of lipoid and seemed longer and the zone was broader than normal. A single, very small area of acute myocardial necrosis was present in the left atrium. No collagen necroses were found. Renal glomeruli revealed occasional thickening of the basement membranes and partial hyalinization of glomerular tufts was very rarely noticed. The spleen and its arteries were normal.

The retinae showed normal vessels. In the nerve fiber layer of both retinae numerous foci were seen composed of small bodies of eosinophilic, sometimes slightly basophilic, homogenous material. These bodies were globular in shape, 10–15 micra in diameter, and together formed expanding lesions disrupting completely the fiber layer and displacing the underlying ganglion cell layer. No inflammatory cells or hemorrhages were seen either in such regions or elsewhere. No papilledema was present (Figure 19).

CLINICAL FEATURES

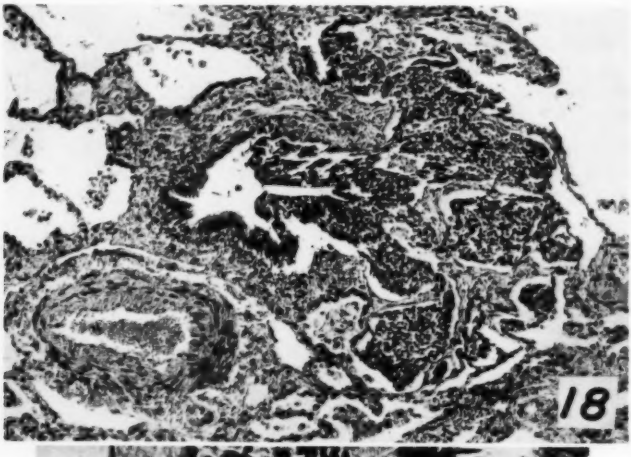
Consideration of the course of the illness of these patients brings to light several clinical points of interest. In all three, the illness was pro-

FIGURE 14. (No. 22206). Hyaline membranes lining distended air spaces with pulmonary edema are seen.

FIGURE 15. (No. 22206). Dense cellular organized exudate is seen plugging alveoli.

FIGURE 16. (No. 22206). Fresh necrosis of bronchiolar mucosa is seen with a polymorphonuclear exudate and damage to the bronchiolar wall.

FIGURE 17. (No. 22206). Organizing bronchiolar exudate is shown as a subsequent phase of the acute lesion pictured in Figure 16.



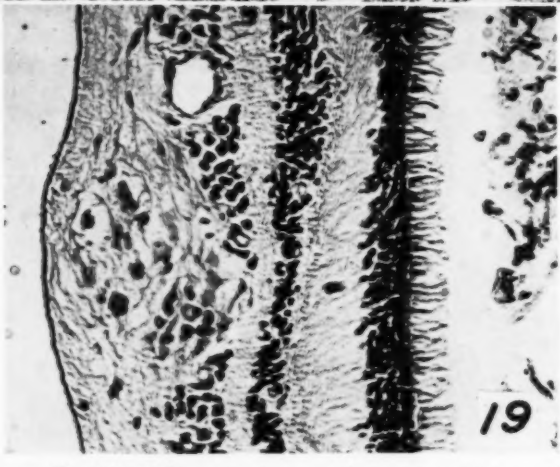


FIGURE 18. (No. 22206). The extensive metaplasia of bronchiolar epithelium extending out into communicating air spaces is demonstrated.

FIGURE 19. (No. 22206). A section of retina with cluster of globular, densely stained cell-like bodies in the nerve fiber layer is shown.

tracted over a period of many weeks. It began insidiously, and the presenting symptoms were so vague in character that it was possible only to approximate their time of inception. In two patients mild weight

loss antedated by several months the appearance of other indications of illness. One patient sought help because of a recurrent psoriatic eruption, complaining only incidentally of mild arthralgia and exertional dyspnea of more recent onset. The other two initially had evidences of a respiratory infection; one a typical "flu" like syndrome. Persistent, severe, hacking paroxysmal cough was a prominent early manifestation in two patients, while the third had only an occasional mild cough, and this not until he had been ill for several weeks. A constant low grade unexplained fever had persisted for several weeks in two patients, associated with progressive anorexia, weight loss, weakness, headache and malaise. One patient had pleural pain, and a pleural friction rub was heard in another. An appreciable though mild degree of exertional dyspnea was common to all at the time of admission.

The principal physical alterations were confined to the chest. Moist medium and coarse rales were a constant abnormality. These were described as being localized chiefly to the basilar portions of the lungs. Rales alone were noted on admission in two patients, but the third had also dullness to percussion, bronchial breathing and bronchophony, and a pleural friction rub. One patient had general glandular enlargement. A skin eruption was prominent in two patients, but in one instance this proved to be psoriasis, and in the other seborrheic dermatitis, both deemed unrelated phenomenon.

Typical cytoid bodies were observed on funduscopic examination of two patients upon admission. They were noted in the third patient a week before his death.

There was a normal white blood cell count in each instance which persisted throughout the illness. The differential blood count remained normal. Two of the patients developed a moderate hypochromic anemia as the disease progressed. The urinary findings were not unusual. One patient had a definite hyperglobulinemia, and in another the plasma globulin was somewhat increased. The electrocardiograms of all three patients showed abnormally low T waves. Extensive bacteriological and other studies were carried out, and all failed to reveal a causative agent. However, it may be significant that the streptococcus MG titre rose and then fell during the course of the illness of two patients.

The radiological alterations observed in the lungs were just as definite as the physical signs early in the course of the illness, but later the

extent of pulmonary infiltration seen in the films far exceeded the manifestations of pulmonary disease disclosed by physical examination.

The striking feature of the clinical course was the progressive increase of pulmonary insufficiency, evidenced by acceleration of pulse and respiratory rates, deepening cyanosis and intensified anxiety. Two patients continued to have a severe cough. In contrast, the third had almost none. Fever was constantly present, the temperature varying from 101 to 103°. As the dyspnea intensified, tachycardia became excessive.

Two patients had severe arthralgia without objective changes in the joints. Both had evidences of nervous system involvement, indicated in one by convulsive seizures, and in the other by combative disorientation. These occurred late in the illness when dyspnea was pronounced.

The appearance of the fundi remained unchanged, the cytoid bodies persisting. None of the patients developed hypertension, significant anemia, increased intracranial pressure or evidence of vascular disease, conditions which are commonly associated with the appearance of retinal cytoid bodies.

All of these patients constituted difficult diagnostic problems. The predominance of dry cough and fever, the moist basilar rales, associated with patches of pulmonary infiltration in x-ray and the normal white blood cell count, initially suggested a virus pneumonia. However, as the illness became more and more protracted, with increasing pulmonary insufficiency, sarcoid and tuberculosis seemed more probable. Finally, the obscure nature of the illness, its duration, the association of a peculiar pneumonitis, fever, arthralgia and cytoid bodies, pointed to a collagen vascular disease.

PATHOLOGICAL FEATURES

The pulmonary abnormalities, similar in all three cases, are somewhat unique. All phases of an unusual pneumonia are seen. The evolution of the acute process can be studied in various parts of the lungs. Slightly older lesions undergoing early repair are seen, while in still other regions extensive organized pneumonia is observed. Almost no normal lung tissue remained. Although the etiological agent was not isolated, certain assumptions seem warranted from a study of the

morphology of the lesions. A viral rather than a bacterial origin is indicated by the acute edema of the air spaces and the interstitial tissues associated with fresh alveolar hemorrhages, the formation of fibrin plugs in alveoli, the hyaline alveolar membranes, the mild mononuclear cell reaction and relative absence of polymorphonuclear leucocytes, and by the lining of the alveolar walls beneath the hyaline membranes or in association with edema by plump elongated cells. Bacterial stains of the tissues showing the most acute changes were negative.

In the classical discussion of influenzal pneumonia during the 1918 pandemic by MacCallum, Wolbach, Goodpasture and Winternitz (1–4), pulmonic lesions similar to the acute changes noted in our three cases were found in patients dying in the first few days of the disease, prior to the appearance of bacteria in large numbers in the lungs. Furthermore, Goodpasture (3) and Parker, et al. (5) have shown that bacteria-free pneumonias, from which the latter workers isolated influenza virus, often presented just such acute morphologic alterations. In more recent years reports have accumulated concerning the pathological anatomy of the lungs of fatal cases of so-called primary atypical pneumonia (6–10). Such lungs presented appearances similar to the acute pulmonary changes described in our cases with minor modifications, including acute edema, fibrinous and hemorrhagic alveolar exudate, formation of hyaline membranes, lining of alveoli by swollen cells, and an essentially mononuclear cell infiltration. The bronchiolar epithelium was sometimes described as being denuded and mucosal necroses were seen. It is also of interest to note that the lesions produced by Muckenfuss, et al., in rabbits by intra-pulmonary inoculation of bacteria-free filtrates of vaccinia virus included many of the acute pulmonary alterations seen in the cases as well as those of influenzal and atypical pneumonia, including the peculiar fresh necroses of bronchial epithelium and walls (11). The gross and histological alterations of the lungs of these patients have also been described as typical changes in cases of psittacosis and ornithosis as well as in the pneumonia of scrub typhus and "Q" fever.

Perhaps the finding of unique interest in the present cases was the widespread fibrous organizations of pulmonary exudates associated with the acute process. Organizing bronchiolitis and extensive metaplasia of bronchiolar and ductule epithelium was associated with the

organized pneumonia in all 3 cases. This extensive change is perhaps related to the long duration of the illness of these patients. Many of the accounts of the various acute pneumonias considered of viral origin have mentioned these organizing exudates, but describe them as a very minor part of the changes. However, the majority of patients with influenzal or atypical virus pneumonia upon whom autopsy was performed had a clinical course ranging from only 1 to 3 weeks. Several illustrations from the monograph by Winternitz on influenzal pneumonia depict fully the organizing and organized changes seen in our cases, although these clearly were not widespread (4). Winternitz commented on the fact that these focal changes had occurred in patients despite the short clinical courses, indicating to him as well as to others that this type of pneumonia might undergo very rapid organization. However, no case with widespread organization was described.

Many of the acute changes described here are characteristic of the so-called anaphylactic pneumonias found in acute rheumatic fever, lupus erythematosus, and others (12). While the degree of fibrous organization of the alveolar exudate present in these 3 patients has not been previously observed in anaphylactic pneumonias, it could probably occur. The complete absence of significant systemic lesions of collagen vascular disease in these cases makes unlikely the possibility that the extensive pulmonic changes were the result of repeated episodes of an anaphylactic pneumonitis. However, it is well recognized that the lesions of collagen vascular disease may be predominantly focal. Several clinical features of the course of illness of these patients suggested disseminated lupus erythematosus. It is possible that they may have had an unusual form of collagen vascular disease with changes confined to the lungs progressing to widespread fibrous organization.

The morphological alterations found in the lungs of experimental animals subjected to various war gases and sacrificed at intervals of time after exposure are somewhat similar to the changes described in these three patients, as well as to other cases of probable or proven viral etiology (13). Chlorine and phosgene in particular may produce bronchial and bronchiolar necroses which progress to organization. Hyaline membranes lining air spaces and a fibrinous pneumonitis which may result in extensive organization have been seen. The ex-

tensive pulmonary edema found in the acute cases is also comparable. These gases, however, often rapidly produce rather extensive tissue necroses which are not duplicated in the viral pneumonias. Furthermore, many of the reports of the changes seen in experimental gassing mention the extensive bacterial invasion leading to lobular pneumonias and abscesses, a change not present in these cases.

In several recent reports on the effects of beryllium poisoning, a chemical pneumonitis has been found to be prominent in the acute cases (14, 15). Van Ordstrand and his associates described five deaths which they considered a result of the inhalation of beryllium dust. These patients clinically had a severe pneumonitis and while the descriptions of the pathological changes in the lungs were meager, the photomicrographs suggest changes similar to those described in these cases as well as of cases of viral pneumonitis in the literature.

The pathological changes observed in the lungs of these three patients illustrate very distinctly all the alterations seen in pneumonias of viral origin, and in addition uniquely present a very striking degree of organization of extensive areas of the affected lungs. It would seem likely from the changes observed in the pathological sections, that these three patients succumbed to pulmonary insufficiency produced by the extensively organized as well as by the fresh pneumonia of probable viral origin.

THE CYTOID BODIES

The finding of cytoid bodies in the fundi of these three patients is an interesting feature of their illness. However, it should be noted that a search of available pathological material disclosed two patients with similar pulmonary alterations in whom cytoid bodies were not demonstrated. These cytoid bodies are white spots of fuzzy outline generally one-fifth the diameter of the optic disc, usually seen only in the posterior portion of the retina. They have the appearance of small cotton pledgets, and for this reason have been called "cotton wool spots." They have been demonstrated to lie in the nerve fiber layer of the retina. While they have a characteristic histological picture, when viewed funduscopically it is not possible to distinguish them from other types of exudative lesions. On microscopic examination the retinal nerve fiber layer is swollen and contains curious cell-like bodies with a central eosinophilic globule. Their origin is still obscure. They were

originally thought to be swollen nerve fibers. Verhoef (16) described cytoid bodies identical with those encountered in various other conditions as occurring in the majority of primary intraneural tumors (gliomas) of the optic nerve. He depicted them as being produced by the distention of a process of a neuroglia cell or neuroglial syncitium with a substance having staining reactions of neuroglial fibers, the connection of this process with the main cell body becoming lost, so that it appears as an isolated structure. In the same vein Martin and Cushing in 1923 thought that cytoid bodies represented masses of coalesced neuroglial fibers. Employing new histochemical techniques, Friedenwald (17) has concluded that a cytoid body represents a peculiar type of cellular degeneration in the nerve fiber layer. He describes the lesion as being regularly located between the terminal bifurcation of a terminal arteriole and having precisely the configuration to be expected if the arterial flow were occluded just upstream from this bifurcation. He concludes that the lesion is a minute ischemic infarct which may result from occlusion of such an arteriole or from transient spasm. In the process of healing which usually requires 2 to 4 weeks, he has observed the disappearance of cytoid bodies as new capillaries grow into the damaged area.

Cytoid bodies are seen in a wide variety of circumstances, and they are not typical of any particular disease entity. They have been decribed as occurring in malignant hypertension, severe anemia, terminal stages of carcinomatosis, periarteritis nodosa, lupus erythematosus disseminatus, leukemia, and in increased cerebrospinal pressure with papilledema and optic neuritis. Maumenee (18) regards them as being a manifestation of generalized toxemia, and he points out that in 1872 Roth was the first to ascribe these bodies as manifestations of generalized septicemia.

A study has been made of the circumstances under which cytoid bodies have been found in 55 patients examined post mortem at the Johns Hopkins Hospital. Table I lists the various illnesses associated with the appearance of these lesions. Clinically, it is important to emphasize that their presence has no diagnostic specificity. However, in the absence of some common cause for the presence of the cytoid body such as hypertensive-renal-vascular disease or septicemia, one must consider some more obscure process.

The significance of the appearance of cytoid bodies in the fundi of these three patients with diffuse pulmonary disease is not apparent. Duke Elder and others have stressed that retinal changes are not uncommon in almost any infectious disease process, including influenza

TABLE I

The Occurrence of Cytoid Bodies in 55 Autopsied Patients

A. *Degenerative Vascular Disease:*	
1. Arteriosclerosis	2
2. Arteriosclerosis and diabetes	2
3. Arteriosclerosis and anemia	1
4. Hypertensive cardiovascular renal	22
5. Hypertensive cardiovascular and diabetes	4
B. *Anemia:*	
1. With unexplained leucopenia and thrombopenia	1
2. With carcinoma of the stomach	1
3. With carcinoma of the gall bladder	1
4. With hypernephroma	2
C. *Increased Intracranial Pressure:*	
1. Glioblastoma	1
2. Medulloblastoma of cerebellum	1
3. Glioma in corpus callosum	1
4. Metastatic carcinoma of the lung	1
5. Metastatic hypernephroma	1
6. Meningitis with sinus thrombosis	1
D. *Collagen Disease:*	
1. Lupus Erythematosus Disseminatus	2
E. *Blood Stream Infections:*	
1. Subacute bacterial endocarditis	1
2. Acute bacterial endocarditis	3
3. Septicemia	3
F. *Miscellaneous:*	
1. 37 C.F. with widespread metastases to pleural surfaces of lungs from carcinoma of the breast.	
2. 54 W.F. with hemiplegia, rheumatic heart disease with mitral stenosis, thrombi in left auricle, marked chronic passive congestion.	
3. 40 C.F. with obstruction of vena cava due to carcinoma of the thymus.	
4. 68 W.F. with ? interstitial pulmonary fibrosis.	

(19). The possible causal relationship of some virus infection to the pulmonary lesion of these three patients has already been emphasized. It has been pointed out that none of these patients had clinical or other evidences of a vascular disease, a significant anemia, increased intracranial pressure or septicemia, which might account for the changes

in the fundi. Nor could anoxemia resulting from pulmonary insufficiency have given rise to the cytoid bodies, as they appeared at an early period of the illness when there was no evident anoxemia.

SUMMARY

An account has been given of three patients having an illness with similar clinical and pathological features, not hitherto delineated. Beginning insidiously, this illness terminated in death after the passage of many weeks, during which the patients developed progressive pulmonary insufficiency. Fever, weight loss, malaise and cough were present. Cytoid bodies in the fundi and moist basilar rales were the only significant physical alterations. The white blood cell count remained normal.

Roentgenograms demonstrated progressive extension of a diffuse infiltrative process throughout the greater portion of the lung fields. The pathological changes are considered unique. In addition to alterations in the alveoli and bronchial tree, previously ascribed to pneumonitis of viral or anaphylactic origin or intoxication with beryllium or the war gases, there was widespread organization of the affected lung. Typical cytoid bodies were found on microscopic examination of the retinae.

The cause of this illness is obscure. None of the patients are known to have been exposed to toxic materials. No bacteriological agent has been isolated. The systemic alterations generally associated with collagen vascular disease were not present. There are clinical and pathological features of this illness indicating that it represents a peculiar form of virus pneumonitis during which widespread fibrous organization of the lungs takes place. However, an unusual localized form collagen vascular disease progressing to pulmonary fibrosis cannot be excluded.

Attention has been called to these three patients so that other cases will be recognized and studies of the cause of this illness undertaken.

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THE EFFICACY OF MODIFIED ORAL PENICILLIN THERAPY OF PNEUMOCOCCAL LOBAR PNEUMONIA

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In a previous report from one of the hospitals participating in this study (1), the satisfactory results of treatment of pneumococcal lobar pneumonia with intermittent parenteral doses of penicillin at twelve hour intervals were set forth. In addition the results of treating a selected group of patients with oral penicillin therapy at 12 hour intervals have been described (2). Because of the practical disadvantages of repeated parenteral therapy and the objections to oral therapy, it was felt desirable to examine the relative efficacy of modified oral therapy with penicillin. To insure the rapid achievement and maintenance of an adequate blood level of the drug in patients receiving oral medication, a single initial intramuscular injection of penicillin was given and p-(di-n-propylsulfamyl)-benzoic acid ("Benemid") (3)*, a drug decreasing the renal excretion of penicillin, was administered throughout the course of treatment.

METHOD OF STUDY

The study included all patients admitted with the clinical diagnosis of lobar pneumonia to the general medical wards of the Baltimore City Hospital, the Johns Hopkins Hospital, and the U. S. Marine Hospital during the period January to July, 1950. The following laboratory studies were carried out on admission on all patients: X-ray of chest, blood culture and a study of the sputum by direct smear, Quellung reaction, culture and mouse inoculation.

The patients were divided into two comparable groups, one receiving the modified oral regimen, and the other intermittent intramuscular penicillin. All

* The Benemid and penicillin used in this study were supplied through the courtesy of Sharp and Dohme.

patients whose history number ended with an odd integer received the modified oral treatment (Schedule A), and those with an even integer received intramuscular penicillin (Schedule B).

Patients on Schedule A received 300,000 units of sodium penicillin G in aqueous solution intramuscularly at the time of admission, together with 1.0 gram of Benemid by mouth. At the next 8 o'clock treatment period (A.M. or P.M.) and every 12 hours thereafter, 300,000 units of penicillin G were given by mouth with 1.0 gram of Benemid. Treatment was continued until the rectal temperature was below 99.6°F. for 72 hours. Patients on Schedule B received 300,000 units of sodium penicillin G in aqueous solution intramuscularly at the time of admission, at the next 8 o'clock treatment period (A.M. or P.M.), and every 12 hours thereafter, until the rectal temperature was below 99.6°F. for 72 hours.

During the course of illness the following observations were made: rectal temperature every 4 hours; white blood cell count daily until normal, then twice weekly; hemoglobin estimation on days 1 and 2, then twice weekly; urinalysis on days 1, 2, and 3, then twice weekly; x-ray of chest before discharge or as otherwise indicated.

All patients who were admitted with a clinical diagnosis of pneumococcal lobar pneumonia were included initially in this study. Those in whom this diagnosis could not be substantiated by the isolation of a pneumococcus and the demonstration of lobar consolidation by x-ray were excluded subsequently from the reported series.

RESULTS

One-hundred patients were studied, 43 receiving oral penicillin with Benemid (Schedule A) and 57 being given intramuscular penicillin (Schedule B). Judged by the criteria listed in Table I, the pneumococcal infections were considered to be of moderate and equal severity in the two groups studied. In both, the therapeutic responses, as shown by Table II, were equally satisfactory.

The only death occurred in the group treated orally. This patient was a 58 year old white male, a chronic alcoholic, who was admitted in stupor on the fifth day of his disease with involvement of the entire left lung. An untypeable pneumococcus and *H. influenzae* were isolated from the sputum. Cultures of blood and spinal fluid were negative. Having failed to respond after 48 hours to the regimen of oral penicillin, he was treated then with large doses of penicillin intramuscularly and 2 gm. daily of streptomycin. Despite these measures he died 4 days after admission. No autopsy was performed.

Complications were rare and distributed equally between the two

TABLE I

Analysis of Clinical Data

DATA	PATIENTS GIVEN ORAL PENICILLIN AND BENEMID (Schedule A)		PATIENTS GIVEN I.M. PENICILLIN (Schedule B)		TOTAL
	No.	%	*No.*	%	*No. or %*
Total patients	43	100.0	57	100.0	100
Male	32	74.4	41	71.9	73
Female	11	25.6	16	28.1	27
Negro	33	76.7	40	70.1	73
White	10	23.3	17	29.9	27
Age of patients:					
Under 40 years	24	55.8	27	47.3	51
40–59 years	14	32.6	22	38.6	36
60 years and over	5	11.6	8	14.1	13
Severity of disease:					
Mild	15	35.1	24	42.1	39
Moderate	19	44.1	20	35.1	39
Severe	8	18.5	10	17.5	18
Critical	1	2.3	3	5.3	4
Duration of illness before therapy:					
1 or 2 days	14	32.6	16	28.2	30
3 or 4 days	19	44.2	18	31.3	37
5 or 6 days	7	16.3	16	28.2	23
Over 6 days	3	6.9	7	12.3	10
Indication of severity:					
Bacteremia	9	20.9	13	22.7	22
Multilobar involvement	10	23.3	17	29.9	27
Leucocytes less than 8,000 per cu. mm	7	16.3	4	7.0	11
Shock	0	0.0	4	7.0	4
Disorientation	7	16.3	10	17.5	17
Jaundice	0	0.0	2	3.5	2
Alcoholism	12	27.9	12	21.0	24
Other complicating diseases*	10	23.3	21	36.7	31
Pneumococcal types:					
1–8	23	53.5	42	73.7	65
Higher types	14	32.6	13	22.8	27
Untyped	6	13.9	2	3.5	8
Patients receiving prior treatment	0	0.0	3	5.3	3

* Cardiac failure, diabetes, liver disease, others.

study groups. In the group treated orally, two patients experienced slow resolution of the pneumonic process. In another patient in whom

treatment was complicated by profuse vomiting, spread of the infection to an adjacent lobe took place four days after the institution of oral therapy. In 3 patients receiving intramuscular penicillin slow resolution occurred. A fourth patient in this group was discovered to have a lung abscess 2 days after admission. This patient, a 60 year old colored female with chronic renal insufficiency and syphilitic aortic valvulitis, had had a productive cough for 3 weeks prior to admission. On the day before admission she had a shaking chill and pain in the left chest. There was evidence of consolidation in the midportion of the left lung

TABLE II

Results of Treatment

DATA	PATIENTS GIVEN ORAL PENICILLIN AND BENEMID (Schedule A)		PATIENTS GIVEN I.M. PENICILLIN (Schedule B)		TOTAL
	No.	%	*No.*	%	*No. or %*
Total patients	43	100.0	57	100.0	100
Duration of fever following start of therapy:					
1 day or less	14	32.6	10	17.5	24
2 days	10	23.3	14	24.6	24
3 days	8	18.5	10	17.5	18
4 days or more	11	25.6	23	40.4	34
Duration of WBC greater than 10,000*					
3 days or less	12	27.9	18	31.5	30
4–6 days	8	18.5	20	35.0	28
7 days or more	15	35.1	11	19.3	26
Complications	3	6.9	4	7.0	7
Deaths	1	2.3	0	0.0	1

* Sixteen patients never had a white blood cell count as high as 10,000 per cu. mm.

field and type 16 pneumococci were cultured from sputum and blood. X-ray of the chest taken the second hospital day revealed an area of radiolucency in the left midlung zone which was proved subsequently to be an abscess. It seems probable that the lung abscess did not represent a failure of treatment, but rather that the abscess had been present prior to the institution of therapy.

DISCUSSION

It has been shown previously that penicillin when given by mouth is an effective agent in the treatment of pneumococcal lobar pneumonia

(4–9). Despite the obvious practical advantages of this mode of administration, there have been objections to its employment in the management of severe infections, although conclusive experimental data to support these objections have not been forthcoming. Chief among these have been the facts that penicillin blood levels after oral administration vary widely, are lower and more slowly attained than after the intramuscular injection of an equivalent dose (10–12). This study was undertaken to determine the effectiveness of a modified oral regimen of therapy designed to obviate these disadvantages. In order to attain rapidly a high penicillin level, the first dose was given intramuscularly. Benemid, an agent inhibiting renal excretion of penicillin, was given concurrently in an effort to maintain a higher concentration of penicillin. This experimental regimen was compared with one of already established effectiveness. The study shows that in addition to its obvious practical advantages this modified oral regimen is apparently the therapeutic equal of treatment with intramuscular penicillin.

From the information obtained by this study, the importance of giving the initial dose of penicillin by intramuscular injection or of employing Benemid cannot be determined. The results of oral treatment alone with penicillin are described in an accompanying paper (2). This point requires further comparative investigation.

There were no untoward reactions to the oral or intramuscular administration of penicillin and no serious reactions to Benemid. One patient had protracted vomiting while taking Benemid. She developed a white blood cell count of 2,600 with 32 per cent polymorphonuclear forms during the course of her illness. Following recovery, Benemid was readministered for one week without lowering of the white blood count. One patient receiving intramuscular penicillin, but no Benemid, also developed a white blood cell count of 2,600 with 41 per cent polymorphonuclear leucocytes. There were no indications in this group of patients of renal damage resulting from the Benemid.

This report gives added support to the growing evidence of the effectiveness of crystalline penicillin G given at infrequent intervals, in the treatment of pneumococcal infections.

SUMMARY

Two comparable groups of patients with pneumococcal lobar pneumonia were treated. Forty-three received one injection of aqueous

penicillin G intramuscularly and then oral aqueous penicillin G with Benemid. Fifty-seven were treated throughout with aqueous penicillin G parenterally. There was no significant difference in the results obtained in the two groups.

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THE TREATMENT OF PNEUMOCOCCAL LOBAR PNEUMONIA WITH ORAL ALUMINUM PENICILLIN

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It was shown clearly by Tillett et al that penicillin in small parenteral dosage (1) and with the injections as widely spaced as 18 hours (2) is effective in treating pneumococcal lobar pneumonia. The satisfactory results obtained at this hospital following intramuscular injections at 12 hour intervals have been described in a previous report (3). Penicillin by mouth results in lower plasma concentrations of the drug than the same dose administered parenterally (4, 5). However, comparable plasma concentrations may be achieved by giving 2½ to 5 times as much penicillin by mouth as by injection (6, 7). The successful oral treatment of lobar pneumonia with a variety of penicillin preparations given by mouth at intervals of 1 to 4 hours has been reported (8–12).

Bohls and Cook (13, 14) have described certain advantages of using aluminum penicillin together with benzoic acid. Flippin and Boyer (15) have recently reported that higher and more sustained plasma concentrations of penicillin followed aluminum penicillin and benzoate by mouth than any of four other penicillin preparations they tested. The plasma level following intramuscular injection was greater after 30 minutes than with an equal dosage of any preparation tested by mouth. However, 3½ hours after oral aluminum penicillin it was as great as that achieved by the same intramuscular dosage of sodium penicillin.

Friedman and Terry (12) have reported the successful treatment of 35 cases of pneumococcal pneumonia with 100,000 units of aluminum penicillin by mouth every 4 hours. Because of the obvious practical advantages of oral over parenteral therapy, and of widely spaced over short intervals between doses, it seems of interest to report the results of treating pneumococcal pneumonia in this hospital with oral aluminum penicillin given at 12 hour intervals.

METHOD OF STUDY

All patients with lobar pneumonia admitted to the Osler Medical Service of the Johns Hopkins Hospital between July 1, 1948 and June 30, 1949 are included in this report. Thirty-seven were treated with oral penicillin alone and 13 additional patients received intramuscular penicillin in addition to or instead of oral penicillin for a variety of reasons to be described below.

The diagnosis was established in each instance, following a careful history and physical examination, by the demonstration of pneumonia by X-ray and of pneumococci in the sputum, by culture and mouse inoculation. The pneumococci isolated were typed whenever possible by the Neufeld Quellung technique. A culture of the blood was taken from each patient at the time of admission. The course of each patient was followed carefully by repeated physical examinations, rectal temperature every 4 hours, a leucocyte count daily, and X-ray examination of the chest whenever indicated.

The patients treated with aluminum penicillin* by mouth were given 300,000 units when the diagnosis was suspected to be pneumonia. An additional 300,000 units was given every 12 hours thereafter until the patient was afebrile for 72 hours. This schedule was rigidly followed irrespective of meal-time.

RESULTS

The clinical data of patients treated orally or parenterally are summarized separately in Table I. It will be seen that the great majority of the patients who received oral therapy were only mildly or moderately ill. A relatively higher percentage of severely or critically ill patients were treated parenterally.

The results of treatment are summarized in Table II. It can be seen that the response to oral therapy alone in this series was entirely satisfactory. Actually there was a higher incidence of complications or death in the parenterally treated patients. However, this may be explained by the greater severity of the disease in that group.

The seven patients with complications in the orally treated series include four who experienced slow resolution and three who developed a secondary rise in fever, but without any evidence of spread of the pneumonia, on the second or third day of oral treatment. All of these latter patients were subsequently treated with parenteral penicillin

* Tablets containing 50,000 units of aluminum penicillin and 0.3 gm. of sodium benzoate were kindly furnished by Hynson, Westcott and Dunning, Inc. through the courtesy of Dr. John H. Brewer.

TABLE I

Analysis of Clinical Data

	PATIENTS GIVEN ORAL ALUMINUM PENICILLIN		PATIENTS GIVEN I.M. PENICILLIN		TOTAL	
	No.	%	*No.*	%	*No.*	%
Total Patients	37	100.0	13	100.0	50	100.0
Male	27	72.9	10	77.0	37	74
Female	10	27.1	3	23.0	13	26
Negro	29	78.4	11	84.7	40	80
White	8	21.6	2	15.3	10	20
Age of Patients						
Under 40 years	29	78.4	7	54.0	36	72
40–59 years	7	18.9	5	38.4	12	24
60 years and over	1	2.7	1	7.6	2	4
Severity of disease						
Mild	22	59.5	5	38.4	27	54
Moderate	9	24.3	2	15.3	11	22
Severe	6	16.2	4	31.0	10	20
Critical	0	0.0	2	15.3	2	4
Duration of Illness before treatment						
Less than 2 days	9	24.3	3	23.0	12	24
2–3 days	20	54.1	5	38.4	25	50
4–6 days	8	21.6	4	31.0	12	24
Over 7 days	0	0.0	1	7.6	1	2
Indications of Severity						
Bacteremia	3	8.1	2	15.3	5	10
Multilobar involvement	9	24.3	3	22.9	12	24
Leucocytes less than 8,000 per cu.mm.	3	8.1	3	23.0	6	12
Shock	0	0.0	0	0.0	0	0
Disorientation	1	2.7	7	54.0	8	16
Jaundice	0	0.0	0	0.0	0	0
Alcoholism	8	21.6	7	54.0	15	30
Other complicating diseases*	4	10.8	2	15.3	6	12
Pneumococcal Types						
1–8	18	48.6	9	69.4	27	54
High types	11	29.7	2	15.3	13	26
Untyped	8	21.6	2	15.3	10	20
Patients Receiving Prior treatment	0	0.0	2	15.3	2	4

* Cardiac Failure, Diabetes, Liver Disease, Others.

and recovered uneventfully. No toxic manifestations attributable to oral aluminum penicillin were observed.

There were 2 patients in the parenterally treated series who developed complications of their pneumonia. One of these was a 38-year

old alcoholic negro male. He was admitted on the second day of his illness with delirium and evidences of myocardial failure. There was consolidation of the left lower lobe and bacteremia, with 500 colonies of Pneumococcus type I per cc. This patient developed empyema despite intensive intravenous or intramuscular treatment with penicillin for seven weeks from the time of admission. The empyema was aspirated repeatedly and he finally recovered. The second patient was a 48-year old alcoholic white male who was admitted on the seventh day of illness with consolidation of the right upper and right lower lobes due to Pneumococcus type III. He had empyema at the time

TABLE II

Results of Treatment

	PATIENTS GIVEN ORAL ALUMINUM PENICILLIN		PATIENTS GIVEN I.M. PENICILLIN		TOTAL	
	No.	%	*No.*	%	*No.*	%
Total Patients	37	100.0	13	100.0	50	100
Duration of Fever Following Start of Treatment						
1 day or less	0	0.0	2	15.4	2	4
2 days	20	54.1	4	30.7	24	48
3 days	6	16.2	0	0.0	6	12
4 days or more	11	29.7	7	53.9	18	36
Duration of WBC greater than 10,000						
3 days or less	19	24.3	3	23.0	22	44
4–6 days	12	32.4	3	23.0	15	30
7 days or more	3	8.1	3	23.0	6	12
Complications	7	18.9	2	15.4	9	18
Deaths	0	0.0	2	15.4	2	4

of admission and was treated for 6 weeks with intramuscular penicillin. In spite of this, he developed atelectasis and a lung abscess which subsequently necessitated pneumonectomy and eventual recovery.

The two patients who died were both alcoholic negro males, each with 3 lobes consolidated due to Pneumococcus type I and III, respectively. There was also a bacteremia with 250 colonies of Pneumococcus type I per cc. in the first case. Both patients were in shock and delirious and both had leucopenia below 5,000 WBC per cu. ml. They died 8 and 12 hours after admission in spite of immediate parenteral treatment with penicillin.

The 13 patients were not treated by the oral regimen for a variety of reasons. Three were given intramuscular penicillin by mistake, two had already received intramuscular treatment at the time of admission; two were unable to swallow because of vomiting or delirium; and six, including the 4 described above, received parenteral treatment from the onset because of the obvious severity of their infection. It is impossible to say that these six patients would not have done as well on oral therapy, but at the time it seemed inadvisable to risk a possible delay in the beneficial effects of penicillin by withholding immediate parenteral treatment.

To avoid the possible hazard of delayed penicillin absorption by severely sick patients, it seemed advisable to adopt a modified routine of treatment which would combine an initial parenteral injection with continued oral therapy. The therapeutic results of such a regimen are described in the accompanying paper (16).

SUMMARY

1. The results of treating 50 patients with pneumococcal lobar pneumonia are described.

2. Thirty-seven patients received only aluminum penicillin by mouth at 12-hour intervals with good results.

3. Thirteen other patients, most of whom were more severely ill, received crystalline penicillin G parenterally.

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MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY
HURD HALL, MONDAY, DECEMBER 11, 1950

Dr. Fisher: Before we start the regular program I would like to call on Dr. Marshall, who has something to say.

Dr. Marshall: Mr. Chairman, Ladies and Gentlemen—

Dr. Chesney, you have now attained your majority or come of age as a Dean. You undoubtedly recall that twenty-one years ago, on November 1, 1929, you undertook the administrative duties in the School of Medicine connected with the deanship. I have been fortunate in having been associated with you during the whole period of your deanship, so that I can testify to the splendid conduct of that office. You have done a worthy job for medical education; you have stood for the advancement and expansion of medical research; you have been in the true sense of the word the servant of the Faculty, giving without stint of your time to their difficulties, but never assuming an autocratic pose; you have been fair and just in all your dealings.

It is with the greatest pleasure that as the representative of the members—high, low and intermediate in rank—of the School of Medicine, of the School of Hygiene and Public Health, and of the Hospital, I present to you at this Christmas Season a small token of the esteem in which you are held.

On this tray you will find inscribed

To

DEAN ALAN MASON CHESNEY

WITH THE WARM AFFECTION OF HIS COLLEAGUES AT

JOHNS HOPKINS

AND WITH THEIR APPRECIATION OF HIS DEVOTION TO

THE ADVANCEMENT OF MEDICAL EDUCATION AND RESEARCH

NOVEMBER THE FIRST, NINETEEN HUNDRED AND FIFTY

Dr. Chesney: This is a dirty trick! With absolutely no foreknowledge about this, I am caught flat-footed. All I can say is that Dr. Marshall was correct when he read the inscription on the tray. Everything else he said was completely incorrect! I always thought that he was a representative of correct speech and that all of his public utterances could be taken at face value, but from here on in I won't trust a thing he says!

I need not tell you how much I appreciate it. I just can't talk about it. Thanks an awful lot!

Dr. Fisher: Dr. Chesney, that goes for all the rest of us, too.

The first paper on the program this evening is by Dr. G. O. Gey and Dr. F. B. Bang, and will be presented by Dr. Gey.

CELL STRUCTURE. A COMPARISON OF PHASE AND ELECTRON MICROSCOPY

Some of the very remarkable properties of the protoplasm of living cells must be related to the basic structure of the fibrous gels of which it is composed. The free and purposeful movement of the organized structures and of different cell components, all apparently differing in function, can now be studied quite well with advanced methods of physical optics.

By the proper use of phase optics and time-lapse photomicrography, a remarkable comparison of the living cell's composition and structure can be made with similar but fixed structures examined in the same or an homologous cell, at much higher powers, under the electron microscope. A series of lantern slides and a short motion picture were used to illustrate some of the similarities and differences in the structural organization and the behavior of the malignant cell strain of the rat (T-333 Sarcoma) derived from a normal strain (14p, normal areolar tissue fibroblasts) grown in tissue culture.

The motion pictures showed the structural transformations of the very active superficial plasma-gel layer of these cells. Fibrous processes, especially numerous in the normal cells, reveal their long filamentous character and narrow dimensions (some about 0.2 microns in diameter), and their remarkable ability to grow rapidly in crystalline fashion then stiffen and often break or to "deliquesce" into the receding solated base from which they originally appeared. Tiny beads of superficial gel could be seen receding towards the base of these long fibrous processes. Comparable images of them could be found in electron micrographs. Here the stiffer gelated component shows a fibrous structure; whereas, the bead or the basic membrane is finely granular or nearly amorphous in appearance. To date we have not detected any periodicity in the fibrous component. It is found in both the malignant strain and the normal prototype.

Other types of protoplasmic processes were also the objects of study by phase contrast microscopy. There was demonstrated, for example, the ebb and flow of very thin membranous pseudopodia (ruffles) from the cytoplasm, and the relation of these to the fat droplets and the very long mitochondria within the cytoplasm of living cells of a twenty-year-old culture strain of human chondromyxosarcoma. Here again the images studied with phase microscopy could be compared in electron micrographs with comparable regions and structures in these cells, and the detailed pattern could be re-studied and the cell components properly oriented. Thus an interpretation of the cell's ultra-structure, at any point in question, was brought to a reasonable level by first studying the cell in the living state, and then finally as a fixed structure from which electron micrographs could be made and interpreted.

In the thicker regions of cells, where the electron microscope cannot explore except with the aid of ultra-sectioning procedures, some of the differences between the living malignant rat strain (T-333) and its normal prototype (14p) were pointed out in photographs taken with phase microscopy. Considering all the things discussed and illustrated above, a comparison revealed that the malignant cells as found in cultures were found (1) to be thicker, (2) to show a much more prominent ring of fat droplets distributed around the nucleus and the juxta-nuclear area, and (3) to have a much larger juxta-nuclear area, often so rigid as to bend the large nucleus, at least in many of the malignant cells. Also these specific malignant cells were shown to contain a larger nucleus, often several in number and of different size, and more nucleolar material than their normal prototypes. It should also be noted that the malignant cells shown here (T-333) show more of the pinocytosis of Lewis than their normal prototypes. For the first time there was also revealed in the phase motion pictures evidence of a particle excretory mechanism, since droplets could be found to be swept out of the cell by the action of the streaming endoplasm. No attempt was made to provide an explanation of these basic points of difference between these autologous normal and the malignant cells of "isogenic" origin.

Dr. Fisher: We have the same line-up on the second paper, so I think we will save the discussion till after that.

The next paper is by Dr. F. B. Bang and Dr.G. O. Gey and will be presented by Dr. Bang.

THE EFFECT OF THE VIRUS OF EQUINE ENCEPHALOMYELITIS ON CULTURED CELL STRAINS

The virus of eastern equine encephalomyelitis has been grown on some eight lines of rat normal and malignant cells in the same medium of 10% beef extract and 50% human cord serum on glass without a plasma clot.

Three points are made: (1) Within this group of cells there is a wide spectrum of effect. Some lines are promptly killed, others support continued growth and others support little or no growth; (2) Within the intermediate group there may be scattered destruction of cells by virus with continued multiplication of the surrounding apparently healthy cells; (3) An electron microscope study of these infected cells in various degrees of destruction shows a variety of effects ranging from partial destruction of the cellular spikes which Dr. Gey has shown to you, to a progressive eating away of the cytoplasmic structure and a final disintegration of the entire cell.

Our first experiments were concentrated on a comparison of a normal cell (14pf) with its tumor cell derivative T333. The first cell that was shown to be relatively resistant in that infection was either not established at all or remained minimal with no cell destruction and a disappearance of demonstrable infection after a few days. The malignant derivative cell, however, succumbed promptly to a minimal inoculum of the virus and yielded a large amount of virus throughout the short

period of cell survival. These two cell lines present the extremes of the picture. Other cell lines presenting an equal degree of susceptibility are a normal rat fibroblast derived from muscle and a human tumor cell line. It might be well at this point to emphasize the fact that it is impossible to tell if all of the cells in a virus infected culture are actually dead. From the center of a colony in which all of the cells have turned black, lost their outline and normal refractility and in which growth has ceased, living cells may occasionally be demonstrated by transferring the fragment to new medium or by refreshing the medium frequently. A study of several other cell lines showed that an intermediate type of susceptibility is also characteristic of certain other lines of cells. In these cases, virus and cells multiply continuously together. Some cells may be destroyed, virus in small amounts is continuously present in the supernatant bathing the cells and cell multiplication continues at a good rate so that the colonies must be transferred at the usual intervals and the nourishing supernatant fluid must be replaced.

This takes us to the second point of emphasis, that of focal destruction. All cultures of cells, whether they be specifically infected or not, will show a few degenerating cells. However, in these cell lines of intermediate susceptibility the foci of destroyed cells are frequently much more numerous and as will be shown later, the virus of encephalitis is growing in or on the cells in considerable numbers.

The actual titer of virus, you may note in these cultures, is however about 10^{-2} or 10^{-3} per drop of fluid. This means that there are approximately 2,000 to 20,000 embryo infectious units per ml. If each infectious unit represents a virus particle there are considerably fewer virus particles than cells, perhaps one virus particle for every ten or a hundred cells.

To turn to the electron microscope description of the cell-virus reaction. With some recent technical advances in the field we are able to strip the cells from the inside of the very infected roller tubes that are here under study. Degrees of cell destruction can be clearly pictured. Sometimes a spike coming off the cell seems eaten away by virus with an accompanying local disintegration of that particular spike.

Other cells show closely packed rows of individual virus particles sitting along the thin edge of the partially extended cell. Finally, half of a projecting part of the cell proper may be destroyed leaving the other half of that part morphologically intact. Complete disintegration of the cell is accompanied by a scattering of disintegrated and vesicular components including mitochondria with a residue of these parts including virus stuck to the original locus of attachment of the cell. The apparent variety of pictures and progression of events makes it difficult for us to think in simple terms of infection of a cell, a complete conversion of the cell's metabolism to that of virus production, and then a liberation of new particles.

Dr. Fisher: These papers are now open for discussion. Does anyone have any questions or discussion?

Dr. Grafflin, have you?

Dr. Grafflin: I always learn something when I listen to Dr. Gey, and tonight is no exception. He has shown us some beautiful pictures which have been obtained at the cost of extraordinary patience, devotion, and energy. In an age like this, when everybody is working in so-called cellular physiology and chemistry, I think it is good for us all to be continually reminded of the actual structure of the cells we are talking about.

Dr. Rich: These were beautiful pictures. I am sure that everyone was impressed by their beauty.

Dr. Gey, several things occurred to me that I would like to ask about. One is in relation to the fiber formations in the cells. Is it certain that they are not artefacts? *In vitro* does the streaming of the mitochondria and granules in these cells appear to be guided by such fibres?

Dr. Gey, you mentioned just in passing that malignant cells grow a great deal faster than normal ones. In the earlier days of tissue culture, it was often noted that when malignant cells were grown in the same culture with normal cells, the malignant cells didn't grow any faster than the normal ones. Is the more rapid growth of the malignant cells peculiar to this specific tumor, or do you believe that, as a rule, malignant cells grow faster?

Finally, I would like to ask whether the central area in these cells concentrates vital dyes.

Dr. Gey: Dr. Rich, to answer your first question and the others. In showing these electron micrographs, I hoped they would reveal quite clearly the fact that the fibrous bands correspond to the linear array of protoplasm seen in the living even to the place where they do separate and fan out in brush-like fashion. I meant to imply also that there are active streams of endoplasm and that in this streaming endoplasm one may see the particles of fluid taken from the medium, and also mitochondria, all of which are propelled by the "flow" of this endoplasmic material inside the cell. In the electron micrographs, showing bands of these fibers parallel to one another, this streaming endoplasm situation is revealed quite well. In the selected motion pictures it is actually possible to see the long mitochondria passively moving in different directions yet close together. In another region streams may move in the same direction. Therefore, one gets the impression that a line or barrier of material delineates the oppositely moving streams of endoplasm. This margin would appear to be the fibrous structure. We haven't actually reproduced in electron micrographs this sort of thing that we see in the same living cell. We are convinced from the study of living cells in general that we can see very narrow bands of streaming protoplasm adjacent to other bands which move in the opposite direction. The movement of fluid and fat droplets and the mitochondria is like the traffic in the street which goes in opposite paths, but the cell components appear not to be self-propelled.

In regard to your question on speed of growth in malignant cells, these malignant cells grow much more rapidly than their normal prototype. I would hesitate

to assume any responsibility for a statement on the comparative growth potentialities (normal versus malignant) of other types of cells. If we take into consideration cultured cells from such things as liposarcomas, lymphosarcomas, or other different sarcomas of man or animals, and compare our results of attempts to grow them, we find that we could never have predicted or guaranteed which of these cell types would grow. Actually, we have no real notion of the nutritional requirements of some of these cells, whether they be the normal or the malignant. There are many examples of tumors that grow more slowly than normal cells. There are many examples of normal and of malignant cells that cannot be grown easily in culture. It is important that we make our comparisons only with specifically related cells—the malignant with their normal prototype.

Now, in regard to the enlarged centrosphere (central area) we have not studied the effects of the so-called vital dyes. In these malignant cells which are several days old, or those that remained in cultures without treatment for a longer time, one always finds many more with giant centrospheres than in the normal prototype cell. The latter usually have only small centrospheres and these in only a few cells. In making this comment about the centrosphere, I believe we should not apply it to any other situations which bring into this discussion other unrelated cells. It is important to emphasize that here we are dealing with an autologous situation. A comparison of the cytology and behaviour of normal cells from the diaphragm of the rat with sarcoma cells from the periosteum is, I think, an example of an unfair comparison. In this instance, the malignant cells were derived in culture from a line of normal cells. Any conclusions that we may reach by comparing these must be significant contributions to our concepts of differences between malignant and normal cells. Dr. Lewis, Dr. Ludford, and we ourselves, have observed the living enlarged centrosphere. We have observed, in addition, the bending of the nucleus in malignant cells and have commented on the fact that rarely in these normal fibroblasts (14p) does one see such a picture. This structure, the enlarged centrosphere, is, as you well know, a common thing in an hypertrophied macrophage.

Dr. Fisher: Is there any other discussion?

There is a very good exhibit here that many of you may be interested in seeing after the meeting.

The third paper is by Dr. R. J. Bing.

RECENT STUDIES OF CARDIAC FAILURE WITH RELATION TO THE ACTION OF DIGITALIS

The work presented deals with the effect of cardiac glycosides on left ventricular efficiency and on the residual volume of the right ventricle in man. Coronary blood flow and left ventricular oxygen consumption were determined by the means of catheterizations of the coronary sinus. The efficiency of the left ventricle was calculated as the ratio of work of the left ventricle to its energy cost. The residual volume in the right ventricle was measured by injecting Evans Blue through sev-

eral openings of a double lumen catheter into the right ventricle and by suctioning the dye blood mixture from the pulmonary artery into a photoelectric dye recorder. From the photoelectrically recorded dye dilution curves, the residual volume could be estimated.

It is shown that the efficiency of the left ventricle of patients in cardiac failure is diminished. This is the result of a decrease in work. The myocardial oxygen consumption per unit weight is normal. This finding contrasts with results obtained on the heart-lung preparations, where failure is accompanied by an increase in oxygen consumption per unit weight. The findings suggest that the essential disability of the failing heart is a reduction of the proportion of total energy expended in performing useful work. The residual volume of the right ventricle of patients in failure is significantly elevated (normal 50 cc., in right ventricular failure 500 cc.).

Digitalis and strophanthus preparations increase the work of the failing heart by raising the cardiac output. They have no effect on myocardial oxidative metabolism. Thus they increase the efficiency of the failing heart by raising its capacity for work. In normal man the cardiac glycosides lower left ventricular efficiency by decreasing the work. Again the oxidative metabolism is not affected. Digitalis preparations usually produce a fall in the residual blood volume of the right ventricle. These results indicate that cardiac glycosides act on the myocardium directly and have no effect on the oxidative metabolism of the heart. The work discussed illustrates the importance of studying the action of cardiac glycosides on the contractile proteins of the heart muscle directly.

Dr. Fisher: Is there any discussion of Dr. Bing's paper?

Dr. Harvey: I wasn't quite clear how you calculated the weight of the left ventricle.

Dr. Bing: The weight of the whole heart is obtained from tables by Smith. It is assumed that the left ventricle comprises 52 percent of the total heart weight.

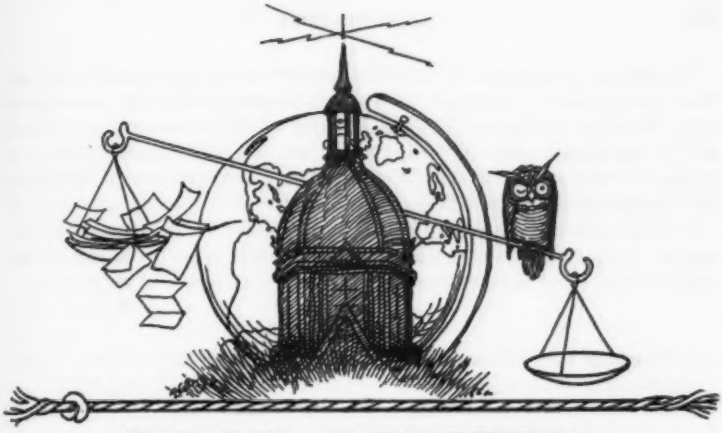
Dr. Harvey: There must be a considerable error in hypertrophied hearts.

Dr. Bing: Yes, there is. However, by using normal heart weights a maximal efficiency is obtained. If this maximal efficiency is low, true values must be even lower.

Dr. Fisher: Is there any other discussion? Dr. King?

Dr. John T. King: Only a word of congratulation and appreciation.

Dr. Fisher: If there is no other discussion, I would like to thank the speakers and call the meeting adjourned.



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Bulletin)

McClung's Handbook of Microscopical Technique for Workers in Animal and Plant Tissues, 3rd edition. Edited by RUTH MCCLUNG JONES. 790 pp. $12.00. Paul B. Hoeber, New York.

This is the third edition of *McClung's Handbook of Microscopical Technique* which first appeared in 1929. The present editor, Ruth McClung Jones, notes in her preface that "there have surely been more changes in the field of microtechnique in the last decades, than in any previous similar period." With this the reviewer agrees. However, the present edition appears to have included only relatively few of the advances which have been made. The majority of techniques which are being employed so successfully today by anatomists and pathologists are for the most part not mentioned. It seems strange, for instance, that at this date no reference is made to Paul Ehrlich, the founder of experimental intracellular chemistry, who utilized the "nadi reagent" to demonstrate indophenol oxidase (cytochrome oxidase) activity. So too, reference to methods for the study of other enzymes such as choline oxidase, lipase, dehydrogenases, glucuronidase, is lacking. Another major contribution to which reference is omitted is the use of enzymes such as desoxyribonuclease and ribonuclease to identify their respective substrates in the nuclei and cytoplasm of cells. Although mention is made of the periodic acid-leucofuchsin technique as a reticulum stain, its application for the demonstration of glycogen and other carbohydrate materials is not to be found. These are some indications of the inadequacy of this *Handbook* in the field of histochemistry. As far as classical staining is concerned it is satisfactory. There have been fewer advances in staining of neurological elements, for instance.

Bennett has contributed an admirable section on the use of polarized light. There are sections on qualitative fluorescence microscopy and the phase microscope. However, discussions of the quantitative ultraviolet absorption technique and of microradiography are unfortunately not included. However, there are sections on the radioautographic technique, on the preparation of tissues for electron microscopy and on microincineration.

It is this reviewer's impression that this volume has not been revised as adequately as current advances in microscopical technique demand. This is a serious drawback, one which detracts considerably from the usefulness of the volume.

R. H. F., Jr.

Cell Physiology and Pharmacology. By J. F. Danielli. 156 pp. $3.00. Elsevier Publishing Co., Inc., New York.

British scientists in their teaching arrangements and cooperative research have the purposeful facility of disregarding departmental boundaries. The advantages of the stereoscopic viewpoint thus provided are easily recognizable in their publications, a good example of which is at hand in this new book of Prof. Danielli. He is a zoologist, at times engaged in pharmacological research and teaching, and from his reflections on the common problems of the biologist and the organic and physical chemists has come this brief, highly readable survey of the relations of cellular biology and drug action. The chapter headings are worth mentioning: The cell as a physico-chemical unit, Possible actions of drugs on surfaces, Membrane permeability and drug action, Enzymes and drug action, Actions of narcotics, Responses of cells on the biological level. These topics are discussed with a minimum of experimental observations yet there are, in the main, sufficient data to mold the argument. The work is definitely not encyclopedic and cannot be used as a source book. It does provide thoughtful correlations on drug actions, using as its working material the elements of a dozen different disciplines.

C. G. Z.

Renal Function. Transactions of the First Conference, Oct. 20–21, 1949. Edited by Stanley E. Bradley. 172 pp. $2.50. Josiah Macy, Jr. Foundation, New York.

This small volume of one hundred seventy-two pages is the record of the first Macy conference on renal function held in New York on October 20–21, 1949. The stated purpose of the conference was to encourage "re-integration of science now artificially fragmented by the isolation of the several scientific disciplines and specialties." The conference group was composed of fourteen members and eleven guests all of whom have contributed to the science of kidney function. The five formal reports which served to launch the discussion were: The Morphological Aspects of Renal Tubular Secretion, Role of Glutaminase in Tubular Processes, Biochemical Aspects of Renal Tubular Transport, The Tubular Secretion of Potassium, and Acid and Water Reabsorption by the Renal Tubules. The scope of the

informal discussion, however, was broadened by the contributions of the various investigators. The text, though somewhat technical, has been well edited and the illustrations are good which, combined with the stimulating material presented, make this work easy and pleasant reading for those with some background in renal physiology. There is little doubt that some integration was achieved, but the more remarkable feature is the unmasking of the deficiencies of present concepts of kidney function which are the chief obstacles to integration of knowledge of renal function.

E. H. D.

Conference on Cybernetics. Transactions of the Sixth Conference, March 24–25, 1949. Edited by HEINZ VON FOERSTER. 209 pp. $3.50. Josiah Macy, Jr. Foundation, New York.

These proceedings are a report of another of the Josiah Macy, Jr. Foundation's efforts to bring communication between the various separate scientific disciplines. It is successful to a gratifying extent. This group includes clinical psychiatry, sociology, physics, mathematics, psychology, cultural anthropology, and ethnology. There are four papers presented from the several separate areas of the field of cybernetics, and the group then attempts to bring their selective points of view to a general understanding and clarification. The group discussions are fascinating in the facility of the interdisciplinary communication and in the fund of additional information which is afforded the entire meeting.

John Stroud's paper, "Psychological Moment In Perception," brought forward his experimental observations on the mechanism of perception gained from a number of media. The effort was not to hypothecate mechanisms, but to report the observational data. The group found much to talk about during, and after, the presentation and the concept of reverberating circuits and feedback was integrated into the explanation in a meaningful way.

Lawrence Kubie presented a paper on "Neurotic Potential and Human Adaptation," contributing his wealth of clinical experience in acute observation of human behavior to the formulation of a theory of normal and pathological behavior. The group was able to incorporate these data readily, and a critical appraisal of psychoanalysis resulted.

Heinz Von Foerster presented the "Quantum Theory of Memory." It involved considerable mathematic explanation, but the narrative which ran with it, in most instances, was able to give a clear account of the reasoning which would permit one to follow without the ability to comprehend the symbols. This discussion had the most difficult task because the distance between the symbols and the observed psychological data was greatest. There was more modification of the presented theory by the discussants here than in the other papers. The group considered all possible mechanisms of recall and recognition—an excellent possibility to see current thinking in all the groups.

Norbert Weiner gave the last paper, a short attempt to bring the group up to

date on his work and that of the Bell Telephone Company laboratory on sensory prostheses. This attempt to utilize other modalities of sensation to give information comparable to sight for the blind and of sound for the deaf shows heartening progress. The discussion was limited to information questions.

A. R. M.

Principles of General Psychopathology. An Interpretation of the Theoretical Foundations of Psychopathological Concepts. By SIEGFRIED FISCHER. 327 pp. $4.75. Philosophical Library, New York.

This attempt to reformulate the theoretical concepts of psychopathology may be of interest to those concerned with surveying or studying variant approaches to the subject. The book and its concepts are of limited value in clarifying psychopathology. The orientation, generally derived from the academic German tradition, does not further the genetic-dynamic psychopathology which forms the foundation for contemporary psychiatry. Part of the difficulty seems to lie in the confused terminology and lack of consistent focus or organization. Even judged in its own tradition, it does not appear to the reviewer to add clarity or depth.

J. S.

Eyes and Industry, 2nd edition. By HEDWIG S. KUHN. 378 pp. $8.50. The C. V. Mosby Co., St. Louis, Missouri.

This volume is the second edition of Dr. Kuhn's book which was well known to ophthalmologists under its former title of "Industrial Ophthalmology." The first four chapters deal with the essentials of a modern industrial eye program. The modern visual testing procedures are described, together with the advantages and limitations of the battery test instruments, tele binocular, the ortho-rater and sight screener. The pattern of visual skills required by a variety of industrial occupations is discussed at length and this portion of the text is illustrated by pictures of workers at occupations requiring unusual visual skills. Dr. Kuhn then outlines a program for the correction of visual defects found.

Dr. Albert C. Snell has contributed the fifth chapter, a discussion of the industrial eye injuries from solid bodies. The next six chapters deal with specific problems of industrial ophthalmology, the effects of radiant energy on the eye, chemical eye injuries, and illumination. A particularly valuable chapter is that on eye protection including much information on goggles which is not readily available elsewhere. Each chapter is followed by a complete list of references.

The book should be most useful to ophthalmologists practicing in industrial communities.

E. U. O.

The Care and Breeding of Laboratory Animals. Edited by EDMOND J. FARRIS. 515 pp. $8.00. John Wiley & Sons, New York.

This excellent and much needed compendium gathers together information

from a variety of experts on many different laboratory animals, not only dogs, cats, rabbits and guinea pigs, but even tropical fish, reptiles, amphibia and drosophilia. A professor of poultry genetics tells us about the rearing of chickens and one of the first geneticists to raise pure lines of mice tells us how to care for laboratory mice. All of the chapters are thus both authoritative and informative. They include diverse practical matters, such as tuberculin testing in monkeys, the types of grass best used in aquaria and types of cages needed in each case and where they may be obtained.

Most of the chapters are well balanced. Such is the one by Paul Sawin on the problems of rabbit raising and this includes a brief and fine resumé of the different diseases to which rabbits are susceptible. Other chapters, such as that on the mouse, have practically no information on the natural diseases.

This book is a fine companion-piece to the recent English text in the same general field, Worden's "Care and Management of Laboratory Animals." It would be hard to choose between the two and since the chapters are often so different, probably a copy of each,—certainly the one or the other—should be available to every experimental laboratory where animals are used in any number.

F. B. B.

Color Atlas of Pathology. Prepared under the auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Md. 546 pp. $20.00. J. B. Lippincott Co., Philadelphia, Pa.

This volume was prepared under the auspices of the U. S. Naval Medical School, Bethesda, Md. The Foreword states that "the profession of medicine has for a long time lacked a comprehensive, concise and realistic source of reference (in pathology) with reproductions in full color." Whether one agrees with this viewpoint or not the present volume is certainly not comprehensive and is too concise.

The subject matter is presented on a regional basis which, as is usually the case with such an arrangement, does not help in affording one a complete picture of any one disease. There are in addition glaring omissions: diseases of the breast, endocrine disorders, diseases of the female generative organs and neurological disorders such as brain tumors, multiple sclerosis and poliomyelitis. One gains the impression that the subject material is overly weighted in favor of tumors. Nor is there any general discussion of inflammation, immunity or hypersensitivity. The text which is offered is too concise and resembles more a syllabus than a text. There is no bibliography whatsoever.

At first glance one is overawed by the resplendence of the colored illustrations of which there are 1053 individual figures. Evaluation of these, however, brings one to the inescapable conclusion that black and white reproductions would have served the purpose just as well or even better in the majority of instances. In the first place the size of the illustrations (2¼ x 2¼ inches) is a handicap. With such dimensions relationships which are extremely important are lost. Most of the magnifications are too high which again spoils relationships. Unfortunately too

many of the fields are not particularly well chosen or characteristic. At least this reviewer was unable to recognize certain lesions until the legends were read.

We cannot recommend this book to the medical student and feel it has little usefulness for the post-graduate student. Its price, $20.00, is certainly in excess of its ability to provide "a knowledge of the fundamental pathological principles" as stated in the Foreword.

R. H. F., Jr.

Encyclopedia of the Eye. Diagnosis and Treatment. By Conrad Berens and Edward Siegel. 272 pp. $5.00. J. B. Lippincott Co., Philadelphia, Pa.

This small volume might, not ineptly, be called a cross between a dictionary of ophthalmic terms, and a quiz-compound of ophthalmology. In the short space of 235 pages of large, clear type many hundreds of ophthalmic diseases are defined and treatment outlined. The definitions are somewhat more detailed than those in the conventional medical dictionaries. The treatment advocated, such as it is, is compressed into a few lines. In their preface the authors quite properly apologize for the use of the term "encyclopedia."

The volume will probably be of considerable value to general practitioners and optometrists in that it will give them a quick and concise definition of unknown or unfamiliar terms they may encounter in their correspondence and medical reading. It may give them an inkling of the conventional treatment. It is of course utterly worthless to ophthalmologists, or to students of ophthalmology. In justice to the authors, however, it is improbable they expected it to serve such an end.

A. C. W.

A Syllabus of Laboratory Examinations in Clinical Diagnosis. Edited by Thomas Hale Ham. 496 pp. $5.00. Harvard University Press, Cambridge, Mass.

This syllabus was developed for the teaching of laboratory diagnosis in the Harvard Medical School. The backgrounds and indications for the use of many important laboratory procedures are discussed. Techniques are described briefly but adequately, and emphasis is placed upon the limitations and interpretations of the various tests. In general, laboratory tests are described in relation to the disease states in which abnormal results are encountered. The authors differentiate between routine or basic laboratory procedures and the special tests which are employed only when indicated. A unique section deals with the cost of laboratory examinations. Attention is devoted to the statistical evaluation of the results of certain tests.

The volume is an important contribution in the field of laboratory medicine. Tests of doubtful value, described in profusion in many current texts of clinical pathology, have beem omitted. The information provided is significant, accurate and authoritative and well documented by extensive bibliographic references. There has long been a need for a book of this type. It will serve as a superior text for medical students, but will be equally useful to all physicians who have occasion to perform laboratory tests or to interpret the results of these tests.

C. L. C.

Physiologie und Pathologie des Bilirubinstoffwechsels als Grundlagen der Ikterusforschung. By T. BAUMGÄRTEL, 271 pp. Ganzleinen DM 27. Georg Thieme Verlag, Stuttgart.

This monograph summarizes a series of studies on the metabolism of bilirubin by Dr. Baumgärtel and his associates, in Munich. Baumgärtel's views are quite at variance with current concepts of this subject in the United States. In brief, he believes that urobilinogen and stercobilinogen do not have the same biological significance. The liver secretes into the bile an enzyme which is capable of reducing bilirubin to urobilinogen. This enzyme can be demonstrated in liver brei under anaerobic conditions; the presence of glucose favors the reduction process. However, *in vivo*, reduction of bilirubin occurs not in the liver, but in the gall bladder. This is evident, since hepatic bile is free of urobilinogen. Urobilinogen formed in the gall bladder is absorbed by the small intestine and then destroyed, probably by the liver. It is not, says Baumgärtel, re-excreted by the liver. No urobilinogen reaches the feces. The bilirubin which was not converted to urobilinogen is reduced by bacteria in the large intestine to bilifuscin and to stercobilinogen. Some of this stercobilinogen is in turn oxidized and excreted in the feces as stercobilin. The rest is absorbed through the hemorrhoidal venous plexus, he states, and is excreted in the urine as physiologic sterocobilinogenuria.

In hemolytic anemias, in which excessive blood destruction occurs, there is increased excretion of bilirubin by the liver. Therefore, more sterocobilinogen is formed in the large intestine than normally and stercobilinogen appears in the urine in excess. In parenchymal hepatic disease, on the other hand, the bilirubin derivative which appears in the urine is urobilinogen. These two substances, sterocobilinogen and urobilinogen, can be differentiated by appropriate chemical tests. In obstructive jaundice, the hepatic excretion of the enzyme, which reduces bilirubin, is suppressed. For this reason urobilinogen is not formed, and urobilinogenuria cannot occur.

To buttress his arguments, Baumgärtel refers to an extraordinary number of papers by himself and his students. Unfortunately, in many instances he draws upon the conclusions of these papers without quoting sufficient data. The book is written with an historical approach, and Baumgärtel quotes freely (and I believe not always accurately) from his predecessors in the field. However, there is a dearth of references to the American and English literature, particularly since 1938. The text is most repetitive, and the style is difficult to translate. None the less this book makes stimulating reading, and is sure to have great influence on the development of the subject.

O. D. R.

BOOKS RECEIVED FOR REVIEW

Die Funktionellen Sexualstorungen. By WERNER KEMPER. 102 pp. Kartoniert DM 5.70 ($1.35). Georg Thieme Verlag, Stuttgart.

Encyclopedia of the Eye. Diagnosis and Treatment. By CONRAD BERENS and EDWARD SIEGEL. 272 pp. $5.00. J. B. Lippincott Co., Philadelphia, Pa.

Grundlagen der Gynakologie. Funktionelle Anatomie, Regulationsvorrichtungen Untersuchungstechnik. By HEINRICH MARTIUS. 144 pp. Ganzleinen DM 23.40 ($5.55). Georg Thieme Verlag, Stuttgart.

Methods in Medicine, 2nd edition. The Manual of the Medical Service of George Dock, M.D. By GEORGE R. HERRMANN. 488 pp. $7.50. The C. V. Mosby Co., St. Louis, Missouri.

Muscular Contraction. A Topic in Molecular Physiology. By W. F. H. M. MOMMAERTS. 191 pp. $4.20. Interscience Publishers, Inc., New York.

Natural Childbirth. By FREDERICK W. GOODRICH, JR. 176 pp. $2.95. Prentice-Hall, Inc., New York.

Neurology and Psychiatry in General Practice. Edited by HENRY R. VIETS, in collaboration with C. CHARLES BURLINGAME, CLARENCE B. FARRAR and Z. M. LEBENSOHN. 150 pp. $3.50. Grune & Stratton, Inc., New York.

Pars Pro Toto. Breviarium Medicum Internationale. By ALFRED PEYSER. 196 pp. Kr. 12:- Almquist and Wiksell, Stockholm.

Pharmacological Basis of Penicillin Therapy. By KARL H. BEYER. 214 pp. $4.50. Charles C. Thomas, Springfield, Illinois.

Physiology of the Eye. Clinical Application. By FRANCIS HEED ADLER. 709 pp. $12.00. The C. V. Mosby Co., St. Louis, Missouri.

Physiologie und Pathologie des Bilirubinstoffwechsels als Grundlagen der Ikterusforschung. By T. BAUMGÄRTEL. 271 pp. Ganzleinen DM 27. Georg Thieme Verlag, Stuttgart.

Toxaemias of Pregnancy. Human and Veterinary. A Ciba Foundation Symposium. Edited by JOHN HAMMOND, F. J. BROWNE and G. E. W. WOLSTENHOLME. 280 pp. $4.50. The Blakiston Co., Philadelphia, Pa.